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Nuclear Energy Reserves and Long-Term Energy Requirements[**]

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In this article the world's potential energy reserves are summarized on the basis of available estimates, and the future energy consumption is estimated with the aid of a working hypothesis relating to the growth of the world's population (P) and the energy consumption per capita (γ). According to this estimate, the energy requirements in 30 years will be about seven times and in 80 years about fifty times as high as they are today, and all the concentrated energy sources will be exhausted in about 120 to 160 years. – The energy requirements in the steady state (Pγ = const.) could be of the order of 10^{13} MWh per year and could be met out of magmatic rocks (U,Th) and sea water (U,D). High priority should be given to research and development work on the construction, reliability, and safety of breeder and fusion reactors, the chemical treatment and final disposal of radioactive waste, the extraction of uranium, thorium, and deuterium from the "primitive" raw materials, the relevant problems relating to protection of the environment, and the worldwide control of the excess birthrate.

1. The Problem

Man requires many goods and services to live. These needs must be met by some kind of energy, either in the form of mechanical power or manpower, and in the ultimate analysis, therefore, they find expression in a demand for energy (even money is a form of easily convertible energy[1]). Energy consumption per capita is a guide to the degree of industrialization and the standard of living. In order to view nuclear research and development in its proper perspective, we must ask ourselves how long our reserves of energy sources will be able to meet the requirements of the world's rapidly growing population. To answer this question, our potential energy resources must be compared with our present and future power requirements. The latter will depend on how much the population and the energy consumption per capita increase.

A distinction must be made here between *concentrated* energy sources, which will remain available for use in the near future, and the "primitive sources", which will be called upon to satisfy the long-term requirements of man. The latter consist of uranium and thorium in magmatic rocks, uranium and deuterium in sea water, and solar-radiation-based regenerative power sources. The first question to ask ourselves is how long the concentrated energy sources will be able to meet our demands. Here we find that man is rapidly approaching a steady state which will be characterized by the fact that the product of population and energy consumption per capita ($P \times \gamma$) is constant. Only the primitive raw materials will remain available to meet the energy requirements of man in this steady state, a point which is discussed in Section 5.

We know the following equations to be valid:

$$c = \gamma \times P \tag{1}$$

and

$$C_T = \sum_{}^{\Delta T} \gamma(t) \times P(t) \tag{2}$$

We want to find:

ΔT for $C_T = R$

where R = energy reserves (MWh), c = energy consumption per year (MWh/a), γ = energy consumption per capita per year (MWh $cap^{-1}a^{-1}$), C_T = cumulative energy consumption up to the year T (MWh), P_T = population in the year T (mid-year), T = year, (AD), ΔT = time (in years from 1970) for which the reserves will cover demand, and t = time.

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[**] Based on a lecture delivered on June 5, 1970, at the Kernforschungsanlage Jülich

[1] Cf. *R. Auerbach*, Chemiker-Ztg. *82*, 863 (1958); *91*, 3(1967).

2. Reserves of Concentrated Energy Sources

2.1. Recovery Factor and Efficiency

When considering energy reserves, a distinction must be made between reasonably assured resources (R_{ass}), calculated on the basis of investigations, and additional resources (R_{add}) estimated on the basis of the above and on the basis of general geological and geochemical considerations; the uncertainty regarding the latter is, of course, greater than that of the former. Furthermore, only a part of the available reserves can be recovered. The recoverable fraction of the assured and the estimated additional resources will be called the "potential resources" R (also "estimated ultimate recovery", EUR), and the factor r in

$$R = r(R_{ass} + R_{add})$$

will be called the recovery factor. The latter factor, and therefore also the extent of the potential resources, is dependent on the price that one can afford to pay. Thus, in the case of coal we are faced with the problem of how deep and narrow seams may be before they cease to be workable, and in the case of uranium and thorium of how poor the ores can be before they can no longer be processed. From a purely *technical* point of view there are practically no limits to the recovery of raw materials from very poor sources. An extreme example of this would be plutonium, which was initially separated from uranium in submicroquantities. From an *economic* point of view the richest ores are always exploited first, because they are the cheapest to process. Only when the rich sources are exhausted does it become financially viable to work the poorer sources, because then the materials will fetch high enough prices to cover costs. A decisive factor here is the competition between the energy sources on the market. *Theoretically,* the limit will be reached when the power required for extracting the fuel, *i.e.* for prospecting, recovery, transportation, and conversion of the raw material into the finished product, and conveying it to the place of utilization, in addition to the power equivalent of the total costs of the generating plant, is the same as the usable power that can be produced. The balance between the power expended in production and the power gained on utilization must remain positive, taking into account all losses. For the present purpose consideration should finally be given to the theoretical limiting value of the recovery factor (r_{lim}). This factor must always be less than 1 and may vary a great deal depending on the energy carriers and the deposits.

On average, r is nowadays taken to be ≈ 0.5 for coal and ≈ 0.4 for petroleum. For these raw materials, therefore, the ratio r_{lim}/r is certainly < 2 and thus can be neglected when considering orders of magnitude. The reserves of uranium ore are generally divided up into three price ranges: <25, 25–40, and 40–80 \$/kg U (roughly <10, 10–15, and 15–30 \$/lb U_3O_8). In competition with fossil fuels only the first price range is economically viable today. In the future the prices of the more expensive ores will also be competitive, so that here all three groups will be lumped together. Sources with higher recovery costs are discussed in Section 5; the estimation of r_{lim} will also be of interest in this connection.

As is well known, only a part of the energy content of an energy carrier can ever be used:

$$\text{usable energy} = \eta \times \text{primary energy content}$$

where η is the overall efficiency. Moreover, the efficiency varies depending on the energy carrier and the way in which it is utilized. Efficiencies of up to 80 % can be achieved if use is made of the heat of combustion of coal and oil, and, in the case of the production of electricity by means of water power, they may even exceed 90 %. In the conversion of the heat of combustion into electric power, η is governed essentially by the thermal efficiency which is about 35 %. If nuclear energy is used for the production of electric power, the conversion factor is also involved in the question of efficiency. In nuclear power stations with light-water reactors, the predominant type nowadays, essentially only the uranium isotope U-235 (relative abundance 0.72 %) is utilized; the overall efficiency relative to the total uranium is about 1 %. The development of breeder reactors, in which the bulk of the uranium (U-238, 99.28 %) and all the thorium (Th-232, 100 %) can also be used, is therefore an essential prerequisite for the future of nuclear energy. In breeder reactors the conversion factor is:

$$k = Q/Q_0 > 1$$

where Q_0 = initial quantity of fissionable material (U-235, Pu-239, U-233) in the reactor and the reprocessing plant, and Q = quantity of fissionable material left after a cycle in which the quantity Q_0 has been consumed; *i. e.* all of the uranium or thorium can be utilized. We estimate that, when the bulk of the (U,Th) ores are being used, full utilization will be made of the breeder process, so that the total efficiency, as in conventional power stations, will be governed essentially by the thermal ef-

Table 1. Energy equivalents and other conversion factors.

Unit	Equivalent		Remarks
1 kcal	= 1.162×10^{-6}	MWh	
1 HPh (metric)	= 7.355×10^{-4}	MWh	
1 BTU	= 0.293×10^{-6}	MWh	
1 Q	= 0.293×10^{12}	MWh	1 Q = 10^{18} BTU [2]
1 t h.c.e.	= 8.134	MWh	1 kg hard coal equivalent = 7000 kcal
1 t petroleum products	≙ 11	MWh	varies according to raw material [4]
10^3 m³ natural gas	≙ 10	MWh	"
1 t U	≙ 2.25×10^7	MWh	200 MeV/U atom
1 t Th	≙ 2.30×10^7	MWh	200 MeV/Th atom
1 t D	≙ 6.69×10^7	MWh	5 MeV/D atom
1 short ton U_3O_8	≙ 0.7693	t U	
1 kg U_3O_8	≙ 0.8480	kg U	
1 lb U_3O_8	≙ 0.3847	kg U	
1 short ton ThO_2	≙ 0.7972	t Th	
1 kg ThO_2	≙ 0.8788	kg Th	
1 lb ThO_2	≙ 0.3986	kg Th	
1 lb	= 0.4536	kg	
1 short ton	= 0.9072	t	
1 U.S. barrel (petrol.)	= 0.1590	m³	

ficiency. (The power required for the reprocessing plants will cause a slight reduction in η. On the other hand it will be possible to increase η_{therm} slightly with time.)

Efficiency has been considerably improved over the years. *Putnam*[2] gives the mean global efficiency for all types of energy sources as 0.12 for 1900 and 0.22 for 1947; *Mandel*[3] states that it is now 0.30. This means that the consumption of usable energy has in the last 70 years increased 2.5 times more than the production of primary energy.

For the purpose of comparing the potential energy reserves with energy requirements, both quantities will be calculated in primary energy units, *i. e.* changes in η will not be taken into account, since there are no grounds for expecting an improvement in the present-day mean (0.3) that will have a significant effect on our calculations (factor 2). For thermodynamic reasons there can be no great improvement in thermal efficiency, and the proportion of the power requirements satisfied by electricity obtained from thermal power stations is rapidly increasing. Moreover, as already mentioned, in the case of uranium and thorium we are reckoning with the breeder process being put into use and are therefore taking into account the considerable increase in efficiency that it will bring with it (*Putnam*[2] calculates $\eta \approx 0.36$ for the year 2050 AD).

The unit of energy used throughout this article is the megawatt hour (MWh). Since many other units are encountered in the literature, relevant conversion factors are given in Table 1.

2.2. Estimates of Energy Reserves

Table 2 shows the most recent available estimates of global energy reserves.

The estimates of the oil reserves vary primarily on account of differing assumptions with respect to the recovery factor, which may be pushed up higher than 0.4 when the market situation changes. In particular the future recovery of oil from oil sands and oil shales is primarily a question of costs. For our purposes we have chosen – and this is also true of natural gas and coal – the highest of the estimates available for conversion into primary energy.

Table 2. Estimates of the global potential reserves of energy carriers. R_{ass} = assured reserves; R = potential reserves; r = recovery factor.

Raw material	units	Reserves R_{ass}	Reserves R	Primary energy (10^{12}MWh)	Ref.	Remarks
Crude oil	10^9 t	46	850		[6]	with oil-bearing sand and shale r = ?
		73			[7]	
		82	360		[8,9]	R without oil-bearing sand and shale; r = 0.4
			430		[8,9]	R with oil-bearing sand and shale; r = 0.4
			1200	13	[10]	R including 600 of oil-bearing sand and shale; $r \approx r_{lim}$
Natural gas	10^{12}m^3	38			[7]	
			230		[8,9]	R, low estimate
			340	3	[8,9]	R, high estimate
Coal	10^9t h.c.e.	8600	7600	62	[8,9,11]	r = 0.5
Total				78		
U ores	10^6t U	2.3	5.0	113	[12-14]	< 80$/kg U
Th ores	10^6t Th	0.5	1.2		[12]	< 25$/kg Th
		0.5	1.5	35	[13]	< 25$/kg Th
Total				148		

The potential reserves of uranium and thorium have not yet been adequately investigated, and all data are more or less unreliable, particularly those for thorium. There are no literature data at all for many countries, including China, which together make up 44% of the Earth's solid surface. The actual reserves, particularly those in the higher cost category, may therefore be two to three times higher than the estimates in Table 2.

3. Consumption of Energy

Future energy requirements can be calculated from the increase in world population $P(t)$ and from the development in the average energy consumption per head, $\gamma(t)$.

[2] *P. C. Putnam:* Energy in the Future. Van Nostrand, New York 1953.

[3] *H. Mandel,* Atomwirtschaft *15,* 220 (1970).

[4] *E. Ayres* and *C. H. Scarlott:* Energy Sources – the Wealth of the World. McGraw-Hill, New York 1952.

[5] How Many People Have Ever Lived on Earth? Popul. Bull (Washington, D.C.) *18,* No. 1 (1962).

[6] EEC Bulletin 7–1966, special supplement.

[7] Esso Magazine *1970,* No. 1.

[8] *M. K. Hubbert:* Resources and Man. Freeman, San Francisco 1969, Chapter 8.

[9] *M. K. Hubbert,* Energy Resources for Power Production. IAEA Conference Paper SM-146/1, Aug. 1970.

[10] *G. Bischoff,* Die Erde *1968,* No. 2, p. 115.

[11] *P. Averitt,* U.S. Geol. Survey Bull. *1969,* 1275.

[12] World Uranium and Thorium Resources, Paris (ENEA) 1965.

[13] Uranium Resources, Revised Estimates, Paris, Wien (ENEA/IAEA) Dec. 1967.

[14] ENEA/IAEA Joint Working Party Report on U Resources, in press; cf. IAEA Bull. *12,* No. 3, p. 7 (1970).

3.1. Development of World Population

The historical growth in population is illustrated in Fig. 1. This graph clearly shows the rapid increase, often called the population explosion, that has occurred over the last 300 years and which coincides with the development of science and technology. At present the world population increases by 1.4 million per week, *i. e.* about 70 million per year. Figure 1 is not suitable for extrapolation into the future; a more detailed examination of population dynamics is required.

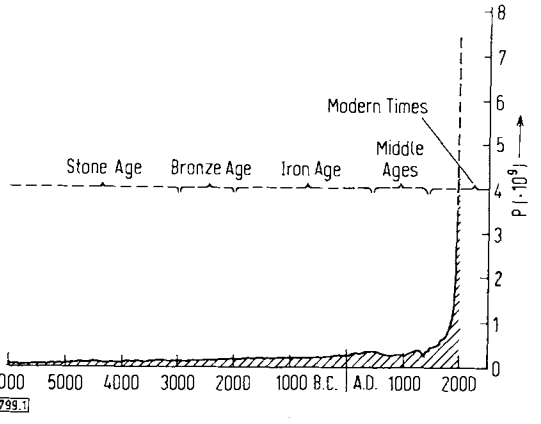


Fig. 1. Growth of world population P since 6000 BC [5].

The change in P (population) with time is expressed by the equation:

$$\frac{\Delta P/P}{\Delta t} = n - m = \varepsilon \qquad (3)$$

where n = natality (birthrate), m = mortality (deathrate), and ε = excess birthrate. Since ε varies with time, we may write $dP/P = \varepsilon(t)\,dt$ or

$$P_t = P_0 \times e^s \qquad (4)$$

$$s = \int_{\Delta t} \varepsilon(t)\,dt$$

Here s = area below the ε curve in the time interval Δt under consideration (dimensionless number). The following equation holds true for time intervals with ε = const:

$$P_t = P_0 \times e^{\varepsilon t} \qquad (5)$$

As an example of population dynamics, Fig. 2 shows the birthrate and deathrate figures for Sweden, an industrial country. Around 1750 the deathrate in Sweden began to fall, and a little later the birthrate also began to decline. The same is true of other western European countries. The graph also shows the corresponding curves for Mexico. Here the decline in the deathrate began at a much later date, but the mortality figures have now dropped to the same level as Sweden's – thanks to the imported "hygienic revolution" and the low average age – while the natality has remained at its previous level. All typical developing countries have been in this phase for about 30–50 years and have undergone a population explosion as a result.

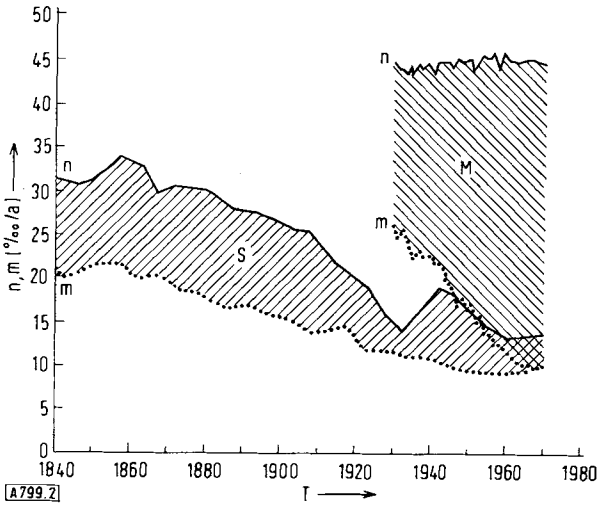


Fig. 2. Natality n (——) and mortality m (· · · ·) in S = Sweden (1840–1968) and in M = Mexico (1930–1968) [15].

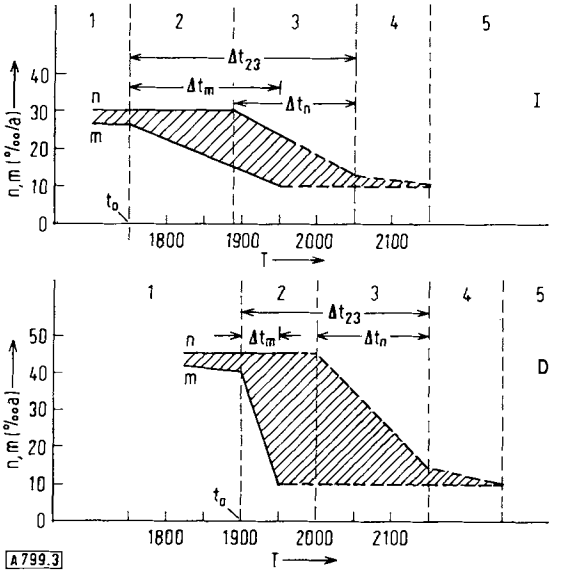


Fig. 3. The phases in population dynamics (schematic). I: industrialized country; D : developing country; natality n, mortality m (see Table 3).

Viewed schematically and as a whole, changes in population can be seen to occur in five phases. These phases are shown in Fig. 3 and Table 3.

Before attempting to anticipate future developments the following must be stated: the population explosion will very soon have to come to a standstill. With ε at its present value of 2%/a the population of the world would be 540×10^9 in 250 years, *i.e.* there would be 4000 in-

Table 3. The phases in population dynamics (see Fig. 3).

Phase no.	Designation	Natality n	Mortality m	Excess birth rate $\bar{\varepsilon}$
1	primitive	high	high	low
2	expansion [a]	high	rapidly falling	rapidly rising
3	regression [a]	falling	falling or low	high and falling
4	prestatic	low and falling	low	low and falling
5	static	constant	constant	constant

[a] Phases 2 and 3 are jointly designated "rationalization phase".

habitants per km^2, a figure typical for present-day cities, and in only 500 years there would be one human being for every square meter of the solid surface. It is obvious that, somehow or other, the population of the world will have to become stationary. The $P(t)$ curve, therefore, like all growth curves in nature will take the form of a sigmoid logistic curve:

$$y = a/(b + e^{-cx})$$

In order to make a prognosis for the future, it is obviously necessary to consider the industrialized and developing countries separately. The expansion phase begins (time t_0) about 150 years later in developing countries than in industrialized countries. The period during which the deathrate declines (Δt_m), however, is reduced from about 200 to about 50 years. It is an open question whether, and if so by how much, the rationalization phase Δt_{23} is also reduced.

A working hypothesis, which allows quantitative predictions, has been postulated by *Fucks*[16]. In order to extrapolate the excess birthrate curves for the developing countries, *Fucks* assumes that the area s under the $\varepsilon(t)$ curve for the developing countries will become equal to the area under the $\varepsilon(t)$ curve for European countries. (This is obviously not the case in Fig. 3, where the area between the n and m curves is considerably greater for the developing countries than for the industrialized countries; taking the *Fucks* hypothesis as a basis, the period of birthrate decline (Δt_n) would have to be very much shorter for the developing countries.) For the area under the ε curve for Europe between AD 1740 and 2020 *Fucks* obtains $s = 1.85$, and hence, using eq. (4), $P_t/P_0 = 6.4$. If the population of the other countries at time t_0 is multiplied by the same factor, then, in accordance with *Fucks*' "hypothesis of equal areas", the world population for the years 2000 and 2050 will be : $P_{2000} = 6.6 \times 10^9$ and $P_{2050} = 9.5 \times 10^9$.

W. Fucks' hypothesis seems to us to be overoptimistic. It is, of course, true that the existence of the old industrial states and effective communications between all countries have considerably shortened the period of deathrate decline Δt_m, but it is unlikely that the expansion and regression phases, *i.e.* the period Δt_{23}, will be similarly shortened. Education is much more difficult to import than hygiene, and the extremely rapidly growing excess birthrate in the expansion phase of developing countries has a feed-back effect which impedes both industrialization and the spread of information and education in family planning.

On account of this, we shall use another working hypothesis to estimate the course of the population growth for the next 130 years. This hypothesis does not take the ε curve for Europe as its starting point; instead, Europe, Asiatic USSR, North America, and Oceania[*] are considered together as industrialized areas. Since North America, Australia, and New Zealand were settled mainly by European emigrants, Europe and these countries must be taken together in order to get an idea of the development of industrialized areas. Asia excluding the USSR, Africa, and Latin America are regarded as developing areas.

Table 4. World population (P) and mean excess birthrate ($\bar{\varepsilon}$) from 1650 to 1970 and distribution on the basis of developing areas (Asia, Africa, Latin America) and industrialized areas (Europe + asiatic USSR, North America, Australia and New Zealand); see Fig. 4.

AD	World		Developing areas		Industrialized areas		Ref.
	P[a] ($\times 10^6$)	$\bar{\varepsilon}$ (%/a)	P[a] ($\times 10^6$)	$\bar{\varepsilon}$ (%/a)	P[a] ($\times 10^6$)	$\bar{\varepsilon}$ (%/a)	
1650	499	0.296	402	0.296	106	0.248	[b]
1700	(580)	0.391	(460)	0.407	(120)	0.405	
1750	705	0.481	564	0.471	147	0.625	[b]
1800	897	0.421	714	0.234	201	0.715	[b]
1820	(980)	0.481	(748)	0.336	(232)	0.848	
1840	(1075)	0.548	(800)	0.389	(275)	0.985	
1860	(1200)	0.663	(865)	0.503	(335)	1.05	
1880	(1370)	0.737	(957)	0.604	(413)	1.05	
1900	1588	0.741	1080	0.629	510	0.934	[b]
1910	(1710)	0.843	(1150)	0.806	(560)	0.906	
1920	1860	1.07	1247	1.10	613	1.01	[18]
1930	2070	1.03	1392	1.17	678	0.741	[18,19]
1940	2295	0.925	1565	1.20	730	0.286	[18,19]
1950	2517	1.77	1766	1.96	751	1.28	[18,19]
1960	3005	1.86	2151	2.15	854	1.08	[18,19]
1970	3620		2660		960		[c]

[a] Figures in brackets: interpolated using the available figures for 1850: 1136×10^6 (world), 829×10^6 (D), 302×10^6 (I): cf. Fig. 5.
[b] Mean value of [2, 20–22].
[c] Figures for 1969 from [19] increased by 69×10^6 (world), 50×10^6 (D), and 19×10^6 (I).

Of course, some of the countries in the areas of the world designated here as developing regions can no longer be counted among the developing countries. On the other hand, not very long ago some countries nowadays regarded as industrialized would have still been considered as developing. In order that we can use the demographic

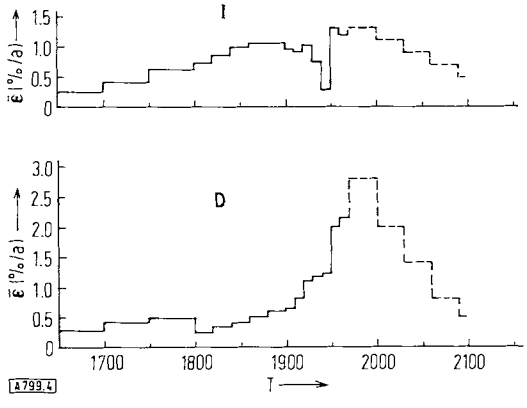


Fig. 4. Mean excess birthrate $\bar{\varepsilon} = n - m$ for industrialized and developing countries from 1650 to 1970 and hypothetical extrapolations (cf. text; see also Table 4).

[*] Comprising mainly Australia and New Zealand.

[15] Population Reference Bureau, Washington D.C.: Population Profile, July 1968.

[16] *W. Fucks:* Formeln zur Macht. Deutsche Verlags-Anstalt, Stuttgart 1965.

[17] Population Reference Bureau, Washington D.C.: Population Data Sheets, 1964, 1966, 1969.

[18] Statistical Yearbooks 1962 and 1969. United Nations, New York 1963 and 1970, resp.

[19] Demographic Yearbook 1967. United Nations, New York 1968.

[20] *A. M. Carr-Saunders:* World Population (Past Growth and Present Trend). Clarendon Press, Oxford 1936.

[21] *W. F. Willcox:* Studies in American Demography. Cornell University Press, Ithaca, N. Y. 1940.

[22] *A. Landry:* Traité de Démographie. Payot, Paris 1949.

statistical material in its present form, these details are not taken into account, since they have no significant influence on the results.

Table 4 gives the corresponding distribution of the global population figures and the mean excess birthrate figures for 1650–1970; the variations of the latter with time are shown in Fig. 4.

As can be seen the $\bar{\varepsilon}$(I) curve has not yet clearly passed its maximum – a result at variance with that obtained by applying *Fucks*' hypothesis – so that the corresponding s(I) value can also be obtained only arbitrarily. Our basis for the extrapolation into the future will therefore be as follows (cf. Table 5):

Table 5. Hypothetical values for $\bar{\varepsilon}$ between 1970 and 2120 for industrialized and developing countries and the resultant population figures P (see also Fig. 5).

AD	Industrialized areas $\bar{\varepsilon}$ (%/a)	Industrialized areas P ($\times 10^9$)	Developing areas $\bar{\varepsilon}$ (%/a)	Developing areas P ($\times 10^9$)	World P ($\times 10^9$)	Remarks
1970		0.960		2.660	3.620	cf. Table 4
2000	1.3	1.4	2.8	6.1	7.5	after ref. [19]
2030	1.1	2.0	2.0	11.0	13.0	
2060	0.9	2.6	1.4	16.7	19.3	calculated on basis of assumed $\bar{\varepsilon}$ values, cf. text
2090	0.7	3.2	0.8	21.3	24.5	
2120	0.5	3.7	0.5	24.7	28.4	

1) For the period up to the year 2000 the latest estimates from the Demographic Center of the United Nations[17] will be used (high estimate).

2) For the period after the year 2000 it will be assumed that the birth excess curves of both the industrialized and the developing countries will fall steeply, namely from their maximum at about the end of this century to $\varepsilon \approx 0.5\%$ at the end of the next (cf. Fig. 4 which, for the sake of simplicity, shows this decrease in step form, the difference between each step being the same).

For reasons given above, this "hypothesis of equal periods" (from the maximum of the $\bar{\varepsilon}(t)$ curves to the beginning of the prestatic, or fourth, stage) seems more plausible to us than the "hypothesis of equal areas". The resultant decrease in the $\bar{\varepsilon}$(D) curve after the year 2000 is very steep, but much less steep – and therefore more realistic – than it would be if it were assumed that the areas under both $\bar{\varepsilon}$ curves had to be the same. As a rational, if only qualitative, basis for the "hypothesis of equal periods" mention should be made of the ever-improving techniques of communication which, of necessity, will lead to a leveling out of the differences. Furthermore, the time available for this leveling process is probably not much shorter but also not much longer, than a hundred years.

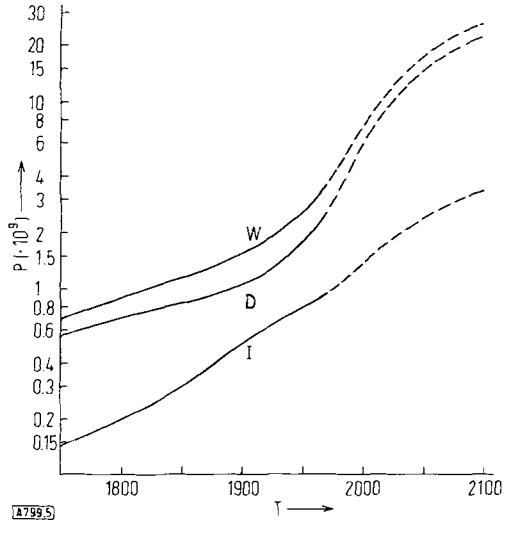


Fig. 5. Growth of the population P for the world, industrialized and developing countries from 1750–1970, and hypothetical extrapolations (cf. text).

On the basis of the above arguments, the world population will be 18×10^9 in the middle of the next century and 26×10^9 at the end of it (Table 5 and Figure 5). The enormous increase in population (to double the present figures in the next 30 years) means that there is also bound to be a rapid growth after the year 2000, since the people maturing sexually after 2000 will be born in rapidly increasing numbers in the 30 years up to the turn of the century. Furthermore, in a rapidly growing population the relative number of women of childbearing age also increases. At present, for example, the proportion of the population under 15 years of age amounts to 25% in Europe, while in Asia it is 35% and in Africa and Latin America it is as high as 43%. Examination of earlier estimates on population development (Table 6) shows that these estimates are invariably rather low.

Table 6. Estimates of population development ($\times 10^9$).

Literature	AD 1950	AD 2000	AD 2050
Pearl and *Reed* 1924 [23]	1.8	1.9	2.0
Pearl and *Gould* 1936 [24]	2.1	2.5	2.6
Carr-Saunders 1936 [20]	2.4	3.7	6.0
Willcox 1940 [21]	2.4	4.0	8.0
Putnam 1953 [2]	-	3.7±0.5	6.3
UN 1957 [25]	-	5.9±1.0	-
UN 1964 [25]	-	6.4±1.0	-
Fucks 1965 [16]	-	6.6	9.5
UN 1969 [18]	-	6.5±1.0	-
used in this paper (Fig. 5)	2.5	7.5	18
de facto	2.5	?	?

3.2. The Development of Energy Consumption per Capita

As Figure 6 shows, there is a close correlation between the annual energy consumption per capita of the population (γ) and the gross national product. A large difference can be seen between the industrialized and the developing countries. The average consumption of commercial energy per head in the USA in 1961 was 70 MWh, *i.e.* 100 to 200 times more than in the areas with the lowest per capita consumption (0.4 to 0.8 MWh). The developing countries therefore have a lot

[23] *R. Pearl* and *L. J. Reed* in *R. Pearl:* Studies in Human Biology. Williams and Wilkins, Baltimore 1924.

[24] *R. Pearl* and *S. A. Gould,* Human Biol. *8,* 406 (1936).

[25] World Population Projections 1965-2000. Popul. Bull. (Washington, D.C.) *21,* No. 4 (1965).

of ground to cover in order to catch up. The average world consumption per capita per year is at present about 14 MWh[18].

The growth rate $\delta = \Delta\gamma/\Delta t$ of world energy production between 1947 and 1968 was 5.1% per year. while the per capita energy consumption between 1953 and 1968 increased by 3.0% per year[18].

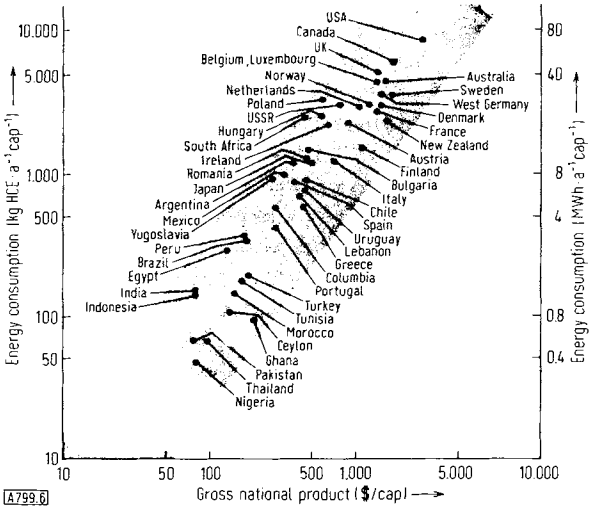


Fig. 6. Consumption of commercial energy per head in comparison with the gross national product in 1961 (after [26], supplemented by the right ordinate in rounded values).

As far as the future is concerned, we must assume that similar growth rates can only be maintained for a relatively short time. With δ at its present value of 3%/a and a population increase of 2%/a the consumption in only 100 years would be 10^{13}MWh per year and in 150 years it would be in excess of 10^{14} MWh/a. All the energy reserves mentioned in Table 2 would then cover only one year's demand. It is clear, therefore, that the growth rate in energy consumption per head, like the growth in population, will have to be reduced in the future. As a working hypothesis for the assessment of this inevitable development, it will be assumed here that the growth rate δ, like the growth rate ε for population on the basis of the "hypothesis of equal periods", will also decrease successively over the next hundred years to values of less than 1%/a, so that the prestatic phase will be reached. For the remaining 30 years of the twentieth century, however, the δ values will probably continue to rise. The high growth rates of the developing countries, arising as a result of their urgent needs (see above), are bound to have a marked effect on the global growth rate, since these countries account for a large proportion of the world's population (72% in 1963 and perhaps more than 80% in 2000).

The δ values given in Table 7 represent a plausible version of this working hypothesis. The world energy consumption per head per year works out at 45 MWh for

Table 7. Hypothetical values for the mean global growth rates of energy consumption per head per year, δ, from 1970 to 2120 and the resultant energy consumption γ, c and C_T.

AD	δ (%/a)	γ (MWh cap^{-1}a^{-1})	c (10^9MWh/a)	C_T (10^{12}MWh)
1970		14	50	4.3
2000	3.9	45	340	10
2030	2.7	100	1300	35
2060	1.8	170	3300	100
2090	1.3	240	5900	240
2120	0.7	300	8500	460

2000 AD. Earlier estimates for the year 2000 have already been corrected upward: *Searl*[27] reckoned on 27, *Bhabha*[28] on 35, and *Mandel*[3] on 43 MWh cap^{-1} a^{-1}. The figure estimated for the USA in the year 2000 is 175 MWh per head per year. After the turn of the century the postulated δ values gradually become lower, indicating a quite considerable decrease in the growth rate of energy consumption and therefore also of industrialization. The resulting γ values are given in Fig. 7. These figures are probably too low rather than too high. Finally from $P(t)$ (Figure 5) and $\gamma(t)$ (Figure 7), we obtain the global yearly energy consumption $c(t)$, as given in Table 7 and Figure 7.

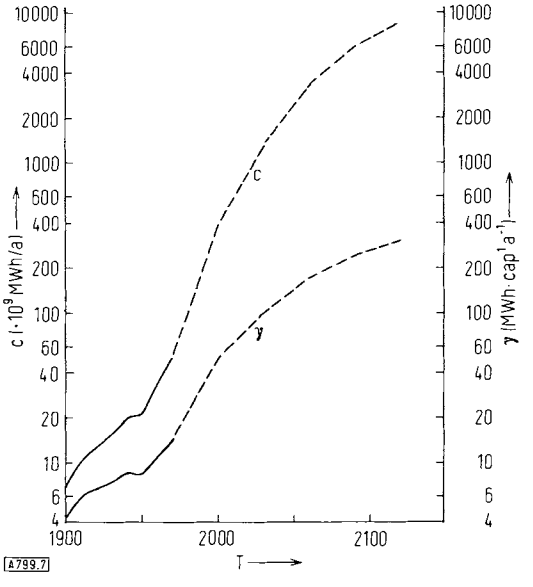


Fig. 7. Energy consumption per head and year, γ, and global annual energy consumption, c, from 1900 to 1970, with extrapolations (cf. text).

4. Comparison of Energy Reserves and Energy Demand

Figure 8 shows the potential energy reserves of the various energy carriers (Table 2). It also shows the cumulative energy consumption as a function of time, as obtained from $c(t)$ (eq.2). In order to normalize the curve, the value of 3.8×10^{12} MWh was chosen, corresponding to the amount of energy which, according to *Mandel*[3], had been consumed up to 1960. (*Putnam*[2] has estimated 6–9 Q, *i.e.* (1.8–2.6) $\times 10^{12}$ MWh for the time from AD 0 to 1860 and a further 4 Q, *i.e.* 1.2×10^{12}MWh, up to 1950 (the energy consumed up to 1860, however, derives mainly from wood and agricultural waste, *i.e.* regenerative energy sources.)

[26] *S. H. Schurr*, Sci. American *209*, No. 3, p. 110 (1963).

[27] *M. F. Searl*, Fossile Fuels in the Future. TID-8209, Oct. 1960.

[28] *H. J. Bhabha* and *M. Dayal*, 3rd Intern. Conference on Peaceful Uses of Atomic Energy, Genève, 28/P/741, 1964.

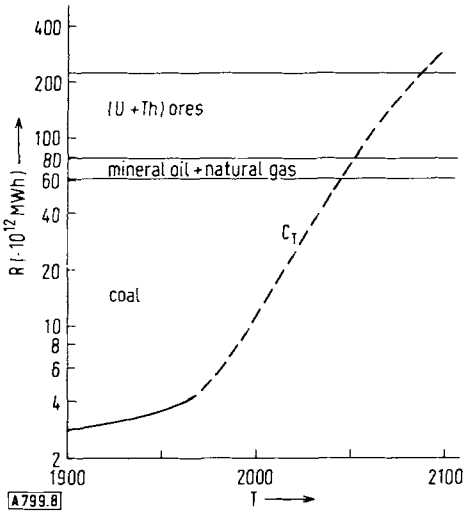


Fig. 8. Potential energy reserves R and cumulative energy consumption C_T (data on global energy consumption: 1900–1950 [2]; 1950–1968: [18]; from 1970 on cf. Table 7).

Comparison of reserves and demand on the basis of Figure 8 leads to the following conclusions:

In the next 30 years man will consume more energy than in all the years since the dawn of human history. The reserves of fossil fuels would suffice, if they alone were used, until 2050, *i.e.* for about 80 years from now.

The estimated potential reserves of uranium and thorium will move this date up to about 2090, *i.e.* they will increase the period only by about 40 years. ΔT, therefore, amounts to about 120 years.

The question posed in Section 1 has thus been answered. We should now ask: How large is the margin of error in this estimate?

It must first be stated that every estimate of ΔT can be meaningful only when based on a reasonably constant further development of the world. Global catastrophes must, therefore, be left out of consideration, even if they are considered likely. Famine and nuclear war apart, however, all predictions for the future, including the present estimates for raw material reserves and our hypotheses relating to $P(t)$ and $\gamma(t)$, must, of course, entail a great deal of uncertainty; they can never be anything more than informed guesses. The result from Figure 8, however, shows that the question posed on the time it will take until all the concentrated reserves are consumed can probably be answered more accurately than to within an order of magnitude, in spite of all uncertainties. On account of the steepness of the $C(t)$ curve an incorrect assessment of the reserves causes only a relatively small change in the period ΔT. If, for example, with a maximum recovery factor, twice the amount of energy carriers could be recovered, *i.e.* 450×10^{12} MWh of primary energy, ΔT would be increased only by 40 years, *i.e.* from 120 to 160 years. Only if the actual reserves exceeded the values used here for potential reserves by one order of magnitude would there be any considerable change in ΔT.

Furthermore, it should be stressed that all three factors were estimated optimistically, in contrast with the normal physical procedure involved in the transmission of errors. In the case of reserves the highest estimates of the potential resources have been used, and the upward correction of the values for uranium and thorium reserves that will probably have to be made will not cause any major changes in the picture. In the case of $P(t)$ the length of the rationalization phase for the developing countries has probably been assessed optimistically. The conjectured decrease in the excess birth rate after the turn of the century presupposes a thorough-going process of enlightenment and measures so rigorous and far-reaching that today they seem scarcely possible in view of all of the opposing factors of a religious, political, and economic nature and the world-wide failure to recognize the problem because of lack of information. Only if the rationalization process succeeds in the coming decades will the prestatic phase be reached in the second half of the next century so that in this period there is not another doubling of the world population. Finally, the prognosis for the energy consumption is probably extremely conservative. It presupposes a quite considerable deceleration in the growth rate of energy consumption per head and therefore in the standard of living after 2000 AD while at present consumption and production are increasing more and more rapidly, both in the planned and in the market economy systems. Furthermore, as is the case with reserves, a change in consumption by a factor of 2 or 3 causes relatively little change in the time ΔT.

Thus, unless the values used for energy reserves and energy consumption prove to be wrong by more than one order of magnitude, ΔT will remain in the order of magnitude of 100 years. Failure to take into account the enormous increase in energy demand as a result of the population explosion and as a result of the even faster growth in the energy demand per head is obviously the reason why ΔT has often been put at thousands or tens of thousands of years and the energy situation has been assessed unrealistically.

5. Energy Requirements and Energy Reserves in the Steady State

As shown above, the present explosion in population and in energy consumption will have to change drastically after the turn of the century and the prestatic phase will have to be reached in the course of the twenty-first century. The estimates of world population in the steady state are all fairly close to each other. Thus, for example, *Watson-Watt*[29] calculates that the figure will probably be 27×10^9 and *Clark*[30] has 45×10^9. Extrapolation of the $P(t)$ curve in Figure 5 indicates a population of between 30 and 40×10^9.

When estimating the energy requirement per head in the steady state, account must be taken of the fact that at this time all the concentrated raw-materials reserves

[29] *R. Watson-Watt*, cited in Internat. Sci. Technol. *1963*, No. 23, p. 98.

[30] *C. Clark* in: Man and his Future. Ciba Found. Sympos., Churchill, London 1963.

of the majority of metals will be exhausted. On the time scale of past and future human evolution the consumption by man of all the raw materials concentrated in ores is only a short episode. After this mankind will have to resort to the very large deposits in the sea and in rocks, which contain metals in very low concentrations. Furthermore, the indications are that desalinated sea water will form the basis of the water supply and that we shall be depending on maximal utilization of the land and sea for food purposes. The energy demand is therefore bound to increase even more. According to Table 7, 100 MWh $cap^{-1}a^{-1}$ will probably be reached in about 60 years and 300 MWh $cap^{-1}a^{-1}$ in about 150 years. With γ_{stat} = 300 MWh $cap^{-1}a^{-1}$ and $P_{stat} = 35 \times 10^9$ the energy demand will be of the order of

$$c_{stat} = 10^{13}\ \text{MWh/a}$$

In comparison, the total energy supplied through solar radiation amounts to 27×10^{13} MWh/a. After the concentrated fossil and fissionable raw materials have been exhausted the "primitive" raw materials mentioned at the beginning of this article will be left to cover the energy demand.

The regenerative energy sources based on solar radiation, according to present estimates (cf. Table 8), can supply some 10^{11} MWh of usable energy, which would only correspond to a few percent of the demand in the steady state.

Uranium and thorium are found as residual crystallization elements in fairly homogeneous distribution in granites and pegmatites at concentrations of 2.7 and 9.6 ppm[31] respectively, *i.e.* about 12 g (U + Th) per ton of rock. To give an example, there is 4.3×10^{12} t (U + Th) in a 1-km thick layer of the crust. According to *Mandel*[32], about 30×10^6 t U and 40×10^6 t Th, *i.e.* a total of about 10^8 t (U + Th), are recoverable (for < 1000 \$/kg U). In the example this would correspond to a recovery factor of 10^{-5}. In terms of primary energy reserves, this amounts to about 10^{15} MWh (Table 9).

The uranium concentration of sea water, according to *Wilson's* measurements[33], amounts to 3.3 μg/l (3.3 ppb), independently of the depth. Local variations are known to occur, and the total number of measurements is small, but the order of magnitude of 1–10 ppb is probably the best estimate for the mean concentration at present available. Since the total volume of sea water is 1.2×10^{18} m^3[34], it follows that the total reserves of uranium in the sea should be those given in Table 9. The thorium content, on the other hand, is so low that it can be ignored. According to *Gupta*[35], there are grounds for hoping that the uranium can be recovered from the sea relatively economically (< 200 \$/kg), perhaps in the way suggested by *Spence et al.*[36]. With the recovery factor value taken as an example in Table 9, the primary energy would be of the order of 10^{13} MWh.

Finally, the total content of deuterium in sea water can be deduced from the accurately known concentration, 156 ppm[37]. Thus, with the very hypothetical value given for *r*, we obtain a value of 10^{18} MWh for the potential primary energy (Table 9).

From the data in Table 9 it follows that the largest resources to meet the long-term requirements of man lie in the uranium and thorium in magmatic rock and, in particular, in the deuterium content of sea water. With the anticipated requirement of 10^{13} MWh/a in the steady state, these reserves could in fact suffice for thousands

Table 9. Reserves of "primitive" raw materials for the production of energy.

Source of energy	Power/m^2 or concentration. resp.	Total reserves (t)	Corresponding energy reserves (MWh)	Maximum recovery factor	Potential useful energy reserves (MWh)
Solar radiation	0.24 kW/m^2	-	2.7×10^{14} p.a.		10^{11} p.a.
U + Th in 1km of earth's crust	12 ppm	4×10^{12}	1×10^{20}	10^{-5}	10^{15}
U in sea	3 ppb	4×10^9	1×10^{17}	10^{-4}	10^{13}
D in sea	156 ppm	1.9×10^{14}	1.3×10^{22}	10^{-4}	10^{18}

Table 8. Estimates on the utilization of solar radiation and geothermal energy.

		Ref.
Mean annual power per m^2	0.24 kW/m^2	[38]
" " " global	3.4×10^{10} MW/cross section of earth	[38]
Energy supplied, global	2.7×10^{14} MWh/a	
Potential useful energy: solar radiation used directly (*e.g.* for heating of buildungs)	127×10^9 MWh/a	[39]
hydroelectric power (2.9×10^6 MW)	25×10^9 MWh/a	[39]
wood, *etc.*	41×10^9 MWh/a	[39]
tides (6.4×10^4 MW)	0.6×10^9 MWh/a	[8,9]
Geothermal (6×10^4 MW)	0.5×10^9 MWh/a	[8,9]
Total	$\approx 200 \times 10^9$ MWh/a	
Other estimate	30×10^9 MWh/a	[2]

[31] *S. R. Taylor,* Geochim. Cosmochim. Acta *28,* 1273 (1964).

[32] *H. Mandel,* personal communication, July 1970.

[33] *J. B. Wilson,* Anal. Chim. Acta *23,* 505 (1960).

[34] *F. F. Koszy* in: Nuclear Geology. Chapman and Hall, London 1954.

[35] *D. Gupta* in *H. Grümm et al.:* KFK 466 (Kernforschungszentrum Karlsruhe), Sept. 1966.

[36] *R. Spence et al.,* Nature *203,* 1110 (1964).

[37] *H. J. M. Bowen:* Trace Elements in Biochemistry. Academic Press, London 1966.

[38] *F. Daniels:* Direct Use of the Sun's Energy. Yale University Press, New Haven 1964.

[39] *H. Brown, J. Bonner,* and *J. Weiz:* The Next Hundred Years. Weidenfeld and Nicolson, London 1957.

of years. Some important reservations should, however, be made:

Firstly, it is doubtful whether the recovery factors in Table 9 represent realistic values. Furthermore, in the case of deuterium, the total efficiency cannot yet even be estimated in terms of orders of magnitude, since the question of the technical realization of fusion reactors remains open.

Secondly, it must be borne in mind that adequate working of magmatic rock and the extraction of deuterium from the sea in sufficient quantities are bound to mean changes in the ecological systems of our environment which cannot yet be visualized. Waste also presents a problem. It seems probable that the heating caused by the $^2/_3$ of the 10^{13} MWh/a evolved as heat for thermodynamic reasons, or the effects on the environment caused by fission products (10^5 t/a for 10^{13} MWh/a) arising from the use of nuclear energy, will set the limit at a considerably lower c_{stat} value.

Thirdly, and most important, the steady state characterized by $P \times \gamma = \text{const.}$ must persist. If P or γ were to increase only by a small amount, not even the enormous reserves of uranium, thorium, and deuterium could cover the energy requirements of man over a long period of time.

From the point of view of energy, therefore, it is imperative that the steady state with a constant population and constant standard of living can be reached. An increasing energy requirement arising from increased difficulties in obtaining raw materials or for the purpose of increasing the standard of living will then be possible only if it is compensated by a reduction in world population.

6. Conclusions

The energy demand in 30 years will be roughly seven times greater and in 80 years roughly 50 times greater than it is today. The potential fossil fuel reserves will suffice – if they are used exclusively – for about 80 years, and the potential concentrated uranium and thorium reserves for roughly another 40–80 years. Thus, optimistic estimates of the potential reserves and conservative estimates of the energy consumption lead to a figure of 120–160 years for the time that will elapse before the reserves of concentrated energy raw materials are used up.

Man is rapidly approaching a steady state characterized in that the population will be restricted by the availability of food and other factors and that the standard of living will be limited by the amount of energy available. The energy requirement in this steady state could be about 10^{13} MWh per year. To cover this demand in the long term it will be necessary to resort to the sources solar and geothermal energy, magmatic rocks, and above all deuterium from the sea.

The bases for these conclusions, namely the estimates of the potential energy reserves, the growth of population, and the development of per capita energy consumption, should be regarded with due caution, and they are offered for criticism. New data on these magnitudes and improved methods of extrapolation (cf., for example, ref.[40]) will from time to time permit improved predictions.

These reflections reach forward to a time which, measured by our own life expectancies, lies far in the future. In fact, however, the estimates have an important bearing on the present: The practice of using the reserves of fossil fuels for the production of heat and electricity should be abandoned as soon as possible, since if enough coal and oil were burned to satisfy the demand it would make the problem of environmental protection almost insurmountable and would probably have prohibitive ecological consequences. Furthermore, these reserves are more valuable, and sometimes indispensable, for other purposes, *e.g.* the manufacture of chemicals and pharmaceuticals, the running of aircraft and automobiles. The development of breeder reactors is an essential prerequisite for the adequate utilization of nuclear fission. Furthermore, the problems of reactor safety must be solved so that nuclear power stations can be operated economically in densely populated areas. This is also true of the chemical problems involved in the treatment and final disposal of the enormous quantities of radioactive waste.

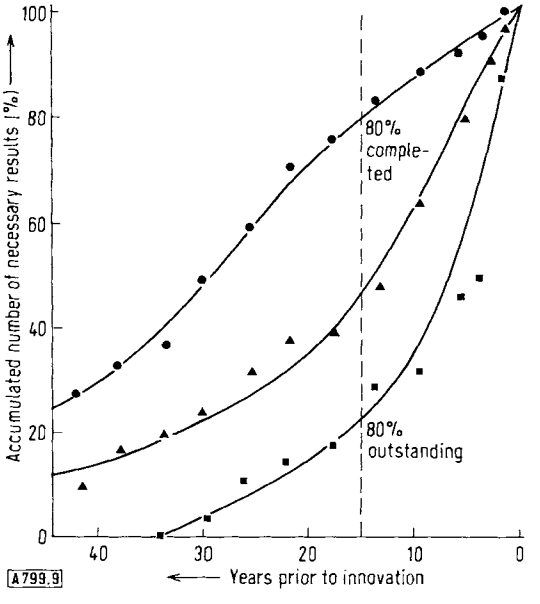


Fig. 9. Number of years of basic research (●), applied research (▲) and development (■) necessary for the realization of innovations (after [41]).

Research and development is of pressing importance for the extraction of uranium, thorium, and deuterium from the primitive raw materials and for the realization of fusion reactors. It takes many years to develop basic innovations, *e.g.* fusion, into technically and economically viable processes (cf. Fig. 9).

[40] United Nations: Future World Energy Needs, IAEA Conference Paper SM-146/50, Aug. 1970.

[41] *G. Friborg*, Forskning och Framsteg (Stockholm) *1969*, No. 3 p. 2.

High priority must be given to all relevant problems of environmental protection, which will probably be the limiting factors in future energy production. Above all, the turning point of the logistic population curve will have to be reached in the coming decades, something which, with all its implications, can scarcely be envisaged today.

Population and energy problems must be solved more quickly than is generally thought. Whether a rational solution is possible depends on what we do or do not do in the next few decades.

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Valence Isomerism in Selected Heterocyclic Systems

By Leo A. Paquette[*]

Valence isomerization and the phenomenologically related principle of valence tautomerism, as they apply to several nitrogen-containing heterocyclic systems, are discussed herein. Attention is called first to 1H-azepines and the reluctance of such substances to isomerize to azanorcaradienes. The role of homo-1H-azepines in this context is then briefly outlined. Azocines (azacyclooctatetraenes) are seen to occupy an interesting position in the sense that pronounced shifts in the position of equilibrium (from almost entirely monocyclic to virtually completely bicyclic) occur with substitutional alterations of various types. The capability of azabullvalenes for degenerate valence isomerization is the next presented, and contrast is made with the properties of benzazabullvalenes and an azasemibullvalene derivative.

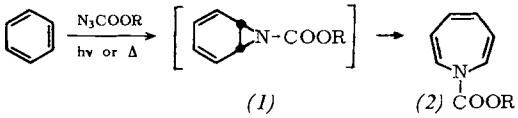
1. Introduction

Valence isomerizations, *i.e.*, those multicenter processes that occur *via* the synchronous (or at least nearly simultaneous) shift of σ and/or π electrons without the intervention of ionic or free radical intermediates, or the migration of atoms or groups, hold a very special position in organic chemistry. By their very nature, such transformations are sensitive to temperature effects, but not to catalytic agents or to wide changes in solvent structure and polarity. When the isomers in question are interconvertible by the surmounting of a relatively low energy barrier, the term valence tautomerism more properly applies. Because of the presence in cyclic polyenes of favorable geometric factors for bond reorganization, such systems commonly exhibit a fascinating propensity for valence tautomerism. Of theoretical significance is the question dealing with the nature of the causative factors that control the various positions of equilibrium as the structure of a given molecule is gradually altered. Customarily, however, a total dissection of the combined structural, electronic, and steric influences is difficult to achieve; as a result, quantitative data for an even wider variety of structural types must continue to be obtained in order to provide a fund of information which will permit the eventual development of sound theoretical principles[1].

In particular, knowledge of the effect resulting from the introduction of a nitrogen atom into various cyclic π-electron networks promised to uncover meaningful information concerning the principles of valence tautomerism. In this review, the behavior of such molecules will be discussed and compared with related hydrocarbon and heterocyclic structures.

2. 1*H*-Azepines

The synthesis of 1-substituted 1*H*-azepines such as *(2)* can be accomplished readily by the photolysis[2,3] or



(1) *(2)*

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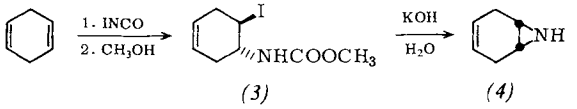
[1] For recent reviews of valence isomerization see: a) *E. Vogel*, Angew. Chem. *74*, 829 (1962); Angew. Chem. internat. Edit. *2*, 1 (1963); b) *W. von E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963); c) *S. J. Rhoads* in *P. de Mayo:* Molecular Rearrangements. Part I. Wiley, New York 1963, p. 655; d) *E. Vogel* and *H. Günther*, Angew. Chem. *79*, 429 (1967); Angew. Chem. internat. Edit. *6*, 385 (1967); e) *G. Maier*, Angew. Chem. *79*, 446 (1967); Angew. Chem. internat. Edit. *6*, 402 (1967); f) *L. A. Paquette* in *J. Snyder:* Nonbenzenoid Aromatics. Vol. 1, Academic Press, New York 1969, p. 249–310.

[2] *K. Hafner* and *C. König*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 96 (1963).

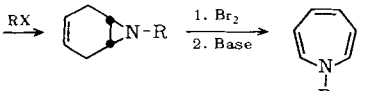
[3] a) *W. Lwowski, T. J. Maricich*, and *T. W. Mattingly jr.*, J. Amer. Chem. Soc. *85*, 1200 (1963); b) *W. Lwowski* and *T.J. Maricich, ibid. 87*, 3630 (1965).

pyrolysis[4–7] of azidoformates in benzene solution. Because singlet nitrenes appear to be involved in the thermal reactions[8], a concerted cycloaddition mechanism leading to intermediate *(1)* is believed to be operative in those cases. The major drawback of the nitrene insertion route is the relative lack of selectivity of nitrenes in their reaction with monosubstituted benzenes. Usually, a mixture of 2-, 3-, and 4-substituted 1*H*-azepines is produced which, in general, defies preparative scale gas chromatographic separation[9–11].

These difficulties can be obviated by means of a synthetic sequence based on the reaction of readily available 1,4-dihydrobenzenes with iodine isocyanate[12]. For example, treatment of 1,4-cyclohexadiene with silver cyanate and iodine in ether, and finally with methanol, produces iodocarbamate *(3)*. Reaction of *(3)* with aqueous potassium hydroxide leads to aziridine *(4)* which has been converted to a variety of functionalized derivatives such as *(5)*. Bromination and dehydrobromination of compounds of type *(5)* provides access to a wide variety of 1-substituted-1*H*-azepines *(6)*.



(3) *(4)*



(5) *(6)*

The isomeric 2-, 3-, and 4-methyl-1-carbomethoxy-1*H*-azepines were likewise obtained in good yield by an identical sequence of reactions commencing with the appropriate 1,4-dihydrobenzene derivatives[12]. Additional studies have shown that the dehydrohalogenation of 3,4-dibromo-7-azabicyclo[4.1.0]heptanes provides a simple scheme for synthesizing many 1*H*-azepines[1f].

The NMR spectrum of 1-ethoxycarbonyl-1*H*-azepine *(2)* (R = C_2H_5) displays a multiplet at δ = 5.3-6.1 due to the six ring protons. The presence of more powerful electron-withdrawing substituents on nitrogen generally results in the appearance of the vinyl protons at lower field[12]. *Günther* and *Hinrichs*[13] have reported a detailed analysis of the spectrum of *(2)* (R = C_2H_5). In Table 1, the spectral parameters for this azepine are contrasted with those for cycloheptatriene.

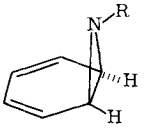
Table 1. NMR/Spectral parameters for *(2)* (R = C_2H_5) and cycloheptatriene [13].

Compound[a]	$\nu_0\delta$[b]	$J_{4,5}$	$J_{3,4}=J_{5,6}$	$J_{4,6}=J_{3,5}$	$J_{3,6}$
(2), R = C_2H_5	35.74	11.44	5.43	0.65	-0.03
Cycloheptatriene	24.42	11.04	5.58	0.68	-0.12

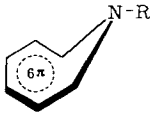
[a] 20 vol % in CCl_4. [b] Relative chemical difference (in Hz) between protons H-4, H-5 and H-3, H-6.

The remarkably close correspondence serves to emphasize the gross structural similarities of the two molecules. Especially noteworthy is the observation that the NMR spectra of a number of 1*H*-azepines remain invariant over a substantial temperature range (−90° to +130°C)[12]. This constancy points to the absence of valence tautomerism of the 1*H*-azepine-azanorcaradiene type.

This conclusion was confirmed by a three-dimensional X-ray study of *(6)* (R = $-SO_2C_6H_4$-*p*-Br)[14]. The molecule clearly exists in a boat conformation; the double bonds are localized at C-2–C-3, C-4–C-5, and C-6–C-7 and the four atoms comprising each double bond and its immediate neighbors are coplanar. Additional molecular dimensions denote substantial sp^2 character for the nitrogen atom. The azepines are therefore true polyenes which exhibit little tendency to exist in the tautomeric azanorcaradiene form *(7)* or as azahomoaromatic entities such as *(8)*.

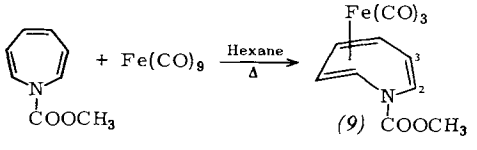


(7)



(8)

The 1*H*-azepines retain their monocyclic character when coupled to an iron tricarbonyl residue such as in *(9)*[12,15,16]. X-ray analysis of *(9)*[14] revealed bond distances which are consistent with a localized double bond at C-2–C-3 and delocalization in the remaining carbocyclic portion of the seven-membered ring. The geometry of the complex is simulated in formula *(9)*.



(9)

The 1*H*-azepine–azanorcaradiene equilibrium is weighted so heavily in the direction of the 8π-electron seven-membered ring that the bicyclic valence tautomeric form is not detected in *(10)* where the positions 1 and 6 are bridged by a tetramethylene chain[12]. Reversal of the equilibrium is seen only when the methylene bridge consists of three members as in *(11)*[12]. These observations

[4] *R. J. Cotter* and *W. F. Beach*, J. Org. Chem. *29*, 751 (1964).

[5] *F. D. Marsh* and *H. E. Simmons*, J. Amer. Chem. Soc. *87*, 3529 (1965).

[6] *L. E. Chapman* and *R. F. Robbins*, Chem. Ind. (London) *1966*, 1266.

[7] *L. A. Paquette, J. H. Barrett*, and *T. Dawson*, unpublished.

[8] *W. Lwowski* and *R. L. Johnson*, Tetrahedron Lett. *1967*, 891.

[9] *K. Hafner, D. Zinser*, and *K.-L. Moritz*, Tetrahedron Lett. *1964*, 1733.

[10] a) *J. E. Baldwin* and *L. A. Smith*, J. Amer. Chem. Soc. *87*, 4819 (1965); b) *89*, 1886 (1967).

[11] *L. A. Paquette* and *J. H. Barrett*, unpublished.

[12] a) *L. A. Paquette* and *D. E. Kuhla*, Tetrahedron Lett. *1967*, 4517; b) *L. A. Paquette, D. E. Kuhla, J. H. Barrett*, and *R. J. Haluska*, J. Org. Chem. *34*, 2866 (1969).

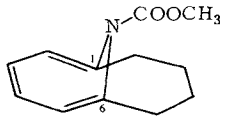
[13] *H. Günther* and *H. H. Hinrichs*, Tetrahedron Lett. *1966*, 767.

[14] *I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett*, and *R. J. Haluska*, J. Amer. Chem. Soc. *90*, 5023 (1968).

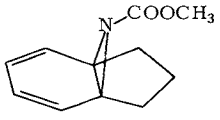
[15] *E. O. Fischer* and *H. Rühle*, Z. Anorg. Allg. Chem. *341*, 137 (1965).

[16] *H. Günther* and *R. Wenzl*, Tetrahedron Lett. *1967*, 4155.

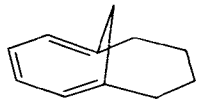
parallel closely the valence tautomeric behavior of bridged norcaradiene derivatives; for example, *(12)* exists exclusively in the cycloheptatriene form[1d,17].



(10)

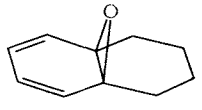


(11)

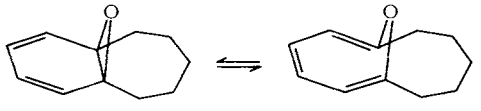


(12)

In contrast, annelated oxepins display concentrations of tricyclic isomers which vary substantially from the above. The substance with a tetramethylene bridge *(13)* exists exclusively in the arene oxide form, whereas the homologous molecule displays spectral properties consistent with the presence of comparable concentrations of *(14)* and *(15)*[1d].

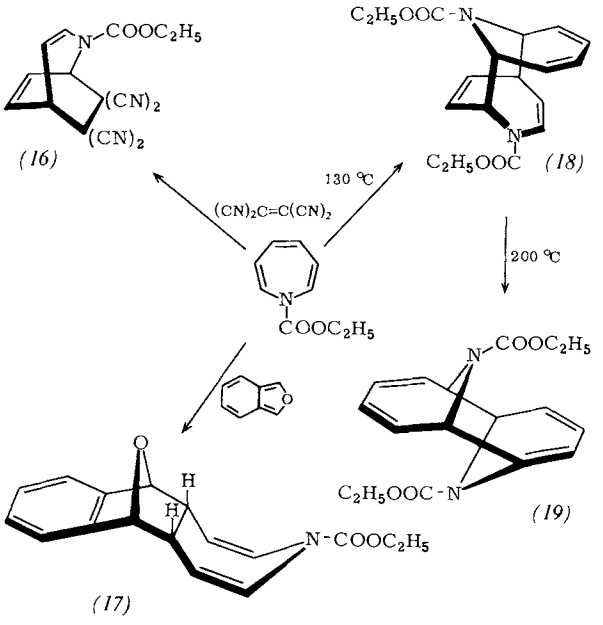


(13)



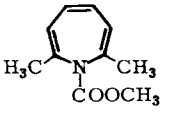
(14) *(15)*

At this point, it becomes very important to single out a significant difference in the chemical properties of 1*H*-azepines, oxepins, and cycloheptatrienes. Whereas oxepins and cycloheptatrienes are capable of ready disrotatory cyclization to the corresponding arene oxides and norcaradienes, respectively, especially in the course of chemical reactions[1d,e,18], 1*H*-azepine derivatives are particularly reluctant to form their related azanorcaradiene counterparts and will do so only as a last resort. For example, cycloaddition reactions and thermal dimerizations of 1*H*-azepines all proceed by way of the seven-membered ring structure except in those instances where steric inhibition precludes normal reaction[19–22].

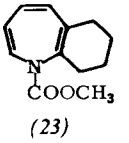


(16) *(18)* *(19)* *(17)*

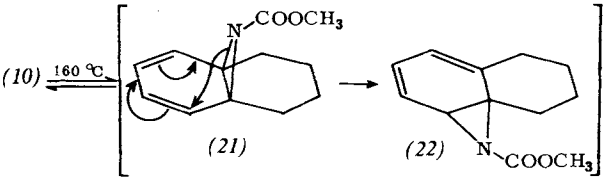
The effect of internal strain on azepine reactivity is perhaps best exemplified by 1-methoxycarbonyl-2,7-dimethyl-1*H*-azepine *(20)* which withstands prolonged heating (24 h) at 200 °C without noticeable dire effects[21]. Thus, although in a formal sense *(20)* contains three conjugated double bonds and is entirely azepine-like in its spectral characteristics, it shows no tendency to dimerize and is not converted to a benzenoid isomer



(20)

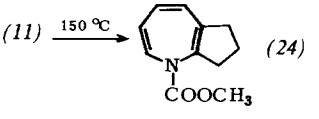


(23)



(21) *(22)*

at elevated temperatures. On the other hand, the closely related annelated azepine *(10)* is cleanly rearranged to the isomeric 1*H*-azepine *(23)* in the vicinity of 160 ° C. Since this behavior is shared by azanorcaradiene *(11)*, the transformation is most readily interpreted on the



(24)

$\Delta H^{\neq}$ = 4.38 kcal/mole

$\Delta S^{\neq}$ = 24.6 e. u.

basis of valence tautomerism of *(10)* to *(21)* which is subject to 1,5-sigmatropic shift of the nitrogen atom and Cope rearrangement as shown[21]. In the absence of such polymethylene brackets, however, 1*H*-azepines exhibit no tendency for 1,5 nitrogen shift.

---

[17] *E. Vogel, W. Wiedemann, H. Kiefer* and *W. F. Harrison,* Tetrahedron Lett. *1963,* 673.

[18] Interestingly, the sole *chemical* indication of the existence of oxepins is the formation of 2-oxabicyclo[3.2.0]hepta-3,6-dienes on photolysis: *L. A. Paquette* and *J. H. Barrett,* J. Amer. Chem. Soc., *88,* 1718 (1966); *J. M. Holovka* and *P. D. Gardner, ibid., 89,* 6390 (1967).

[19] *L. A. Paquette* and *J. H. Barrett,* J. Amer. Chem. Soc. *88,* 2590 (1966).

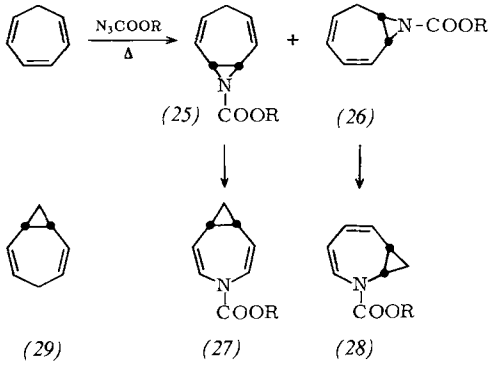
[20] *L. A. Paquette, J. H. Barrett,* and *D. E. Kuhla,* J. Amer. Chem. Soc. *91,* 3616 (1969).

[21] *L. A. Paquette, D. E. Kuhla* and *J. H. Barrett,* J. Org. Chem. *34,* 2879 (1969).

[22] *L. A. Paquette, D. E. Kuhla, J. H. Barrett,* and *L. M. Leichter,* J. Org. Chem. *34,* 2888 (1969).

3. Homo-1*H*-azepines

Treatment of excess cycloheptatriene with an alkyl azidoformate at 125 °C produces a mixture of 1:1 adducts consisting chiefly of *(27)* and *(28)*[23, 24]. These homo-1*H*-azepines are presumably formed by valence isomerization of the initially produced aziridines *(25)* and *(26)*, respectively. The temperature-invariant NMR spectra of *(27)* and *(28)* (40–170 °C) attest to the fact that the internal cyclopropyl bond in these structures is not prone to delocalization or to valence-bond tautomerism. If equilibria of type *(25)* ⇄ *(27)* and *(26)* ⇄ *(28)*



are operative, the concentrations of *(25)* and *(26)* do not rise above the detection limits of the spectrometer (≈ 3%). By comparison, bicyclo[5.1.0]octa-2,5-diene *(29)* is subject to structurally degenerate Cope rearrangement which proceeds rapidly at room temperature[25]; no homooxepin has yet been synthesized.

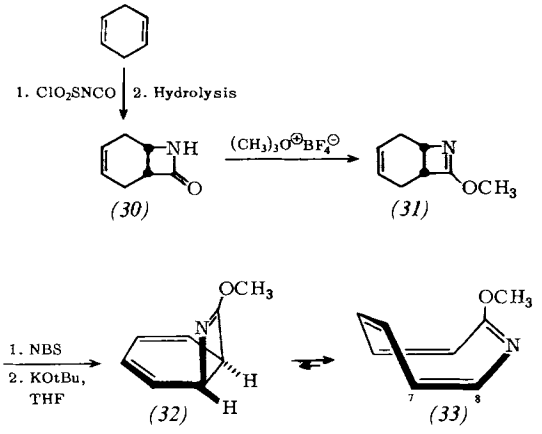
The instability of aziridine isomers *(25)* and *(26)* relative to their homoazepine counterparts parallels the facility with which the thermal valence isomerizations of *cis*-divinyl substituted three-membered rings occur. It is now recognized that the thermal lability of such systems decreases in the order carbon > nitrogen > oxygen > sulfur, with a sizeable gap existing between carbon and nitrogen on the one hand, and oxygen and sulfur on the other[25–28].

The strong bias toward structures *(27)* and *(28)* may be the result of delocalization of the nitrogen electron pair which can only be made manifest in the homoazepines.

4. Azocines

According to *Anderson*'s terminology[29], 1*H*-azepines are considered to be π-excessive nitrogen analogs of cyclooctatetraene. The heteroatom may also be incorporated in π-equivalent fashion, in which case azocines result. In view of the blatant nonaromaticity and marked propensity for unusual structural rearrangement associated with the cyclooctatetraene molecule, unconventional physical and chemical properties can almost certainly be expected to be associated with such monoheterocyclic congeners of this polyene.

Because of the very real possibility that the parent azocine molecule would be so labile as to preclude ready examination of its chemical and physical properties, efforts in this laboratory have been directed to the preparation of 2-alkoxyazocines *(33)*. Such molecules are readily available by way of a highly versatile synthetic scheme based again on the concept of valence isomerization and involving, in its early stages, the monocycloaddition of chlorosulfonyl isocyanate to 1,4-dihydrobenzene derivatives[30–32]. *O*-Alkylation of the resulting β-lactam [*e.g., (30)*] with Meerwein's reagent gives a 1-azetine such as *(31)*, allylic bromination (with *N*-bromosuccinimide (NBS)) and dehydrobromination (with potassium *tert*-butoxide) of which provides the desired 2-methoxyazocines *(33)*.



The NMR spectra of the 2-methoxyazocines are characterized particularly by a low field (δ ≈ 6.5) doublet due to H–8 (when present) and a high field (δ = 4.9–5.1) absorption for H–7. Additionally, the placement of methyl groups on the azocine nucleus does not exert an influence which significantly favors one or more of the possible bicyclic valence tautomeric forms. All of the azocines examined to date exhibit temperature invariant (−75 to 185 °C) NMR spectra which fail to provide any suggestion of the presence of isomeric imidates[33,34]. These observations, in conjunction with the excellent correspondence of their ultraviolet spectra with that of cyclooctatetraene, suggest that these heteroanalogs likewise exist in the strain-free puckered "tub" confor-

[23] a) *L.A. Paquette* and *R.J. Haluska*, Chem. Commun. *1968*, 1370; b) J. Org. Chem. *35*, 135 (1970).

[24] *W. H. Okamura, W. H. Snider*, and *T. J. Katz*, Tetrahedron Lett. *1968*, 3367.

[25] *W. von E. Doering* and *W.R. Roth*, Tetrahedron *19*, 715 (1963).

[26] *E. Vogel, K.H. Oh*, and *K. Gajek*, Liebigs Ann. Chem. *644*, 172 (1961).

[27] *E. L. Stogryn* and *S. J. Brois*, J. Org. Chem. *30*, 88 (1965).

[28] *E. L. Stogryn, M.H. Gianni*, and *A.J. Passanante*, J. Org. Chem. *29*, 1275 (1964).

[29] *A.G. Anderson jr., W.F. Harrison*, and *L.G. Anderson*, J. Amer. Chem. Soc. *85*, 3448 (1963).

[30] *L.A. Paquette* and *T. Kakihana*, J. Amer. Chem. Soc. *90*, 3897 (1968).

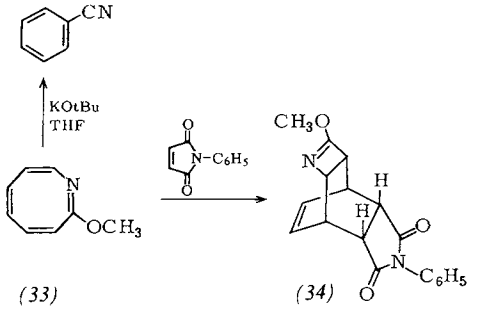
[31] *L.A. Paquette* and *J.C. Philips*, J. Amer. Chem. Soc. *90*, 3898 (1968).

[32] *L. A. Paquette, T. Kakihana, J. F. Hansen*, and *J. C. Philips*, J. Amer. Chem. Soc., in press.

[33] *L.A. Paquette, T. Kakihana, J.F. Kelly*, and *J. R. Malpass*, Tetrahedron Lett. *1968*, 1455.

[34] *L. A. Paquette, T. Kakihana*, and *J. F. Kelly*, J. Org. Chem., in press.

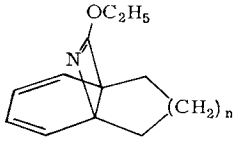
mation known to be preferred by the hydrocarbon[35,36]. Azetine tautomers such as *(32)* are the reacting species in a number of transformations exhibited by the azocines. For example, exposure of *(33)* to potassium *tert*-butoxide for extended periods results in base-induced conversion to benzonitrile[30,32]. Also, cycloaddition of *N*-phenylmaleimide to *(33)* in refluxing toluene leads exclusively to adduct *(34)*. A reversible equilibrium be-



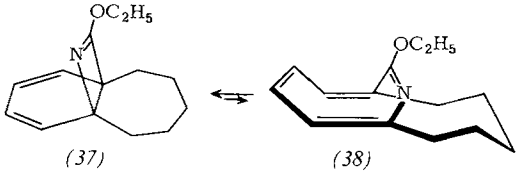
(33) *(34)*

tween the two tautomers *(32)* and *(33)* must therefore exist. Evidently, the 2-methoxyazocines are sufficiently stabilized that the proportion of valence tautomer in equilibrium is below the spectroscopic detection limit ($\leq 3\%$). *Huisgen et al.*[37] have determined that the concentration of bicyclo[4.2.0]octatriene in cyclooctatetraene at 100 °C is 0.01%; there exists, therefore, a parallelism between the two systems.

Because of intensifying interest in the effect of steric influences on valence isomerism, attention was turned to the preparation of a number of annelated 7-azabicyclo[4.2.0]octatrienes. With but one exception[38], the tautomeric capability of unsaturated propellanes possessing a diatomic central bridge has not previously been studied. Taking into account our earlier discussion, it was expected that *(35)* and *(36)* would be totally tricyclic and this was observed[31,32]. Azetine *(37)* was also found to be uniform at room temperature, its spectral properties providing clear evidence for the indicated tricyclic



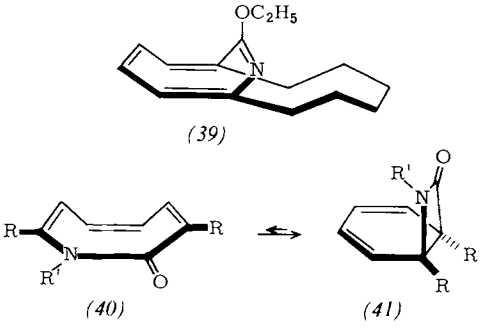
(35), n = 1
(36), n = 2



(37) *(38)*

formation. However, contrary to the behavior of *(35)* and *(36)*, the pentamethylene-bridged heterocycle exhibits a temperature-dependent NMR spectrum. Such changes (which are completely reversible) denote a substantial displacement of the azabicyclooctatriene–azocine equilibrium in favor of bridged azocine *(38)* at the elevated temperatures. Given this information, it was not unexpected to find that imidate *(39)* differed substantially from *(35)–(37)* in its spectral characteristics. Instead, the NMR, UV, and IR absorptions of *(39)* were markedly similar to those of the monocyclic azocines. Thus, it would seem that, when the central bridge of an unsaturated propellane derivative is a small diatomic sp^2-hybridized unit, a chain of six methylene units is required to arrive at a strain-free uniform substance.

Contrary to the behavior of 2-methoxyazocine, 1,2-dihydroazocin-2-one *(40a)* exists predominantly (97–98% at 60 ° C) as bicyclic tautomer *(41a)*[33,34]. Lactam *(40b)* behaves similarly; by comparison with *(40a)*, however, the percentage of monocyclic form was relatively larger



(39)

(40) *(41)*

(a), R = R' = H; *(b)*, R = CH_3, R' = H; *(c)*, R = R' = CH_3

(20%). The effect of a methyl group on the lactam nitrogen of *(40b)* influences the position of equilibrium to an amazing extent. Thus, the NMR spectra of *(40c)* indicated the substance to be entirely bicyclic [*i.e.*, as *(41c)*] over a substantial temperature range.

The presence of an amide function in *(40)*⇄*(41)* has several consequences. First, the strain in the β-lactam portion of *(41)* is not as great as in a 1-azetine ring. Secondly, if one considers the electropositive nature of the carbonyl carbon, a preference for bonding to sp^3 rather than sp^2 hybridized carbon is anticipated for reasons of electronegativity. These factors, in conjunction with a certain amount of stabilization resulting from an increase of diene π-orbital overlap in *(41)*, lead to the prediction that *(41)* should be favored. However, the reasons for this preference are very probably more subtle than outlined, especially when one considers the fact that 1,3,5-cyclooctatrienone is only 7% bicyclic at 60 ° C[39]. Dreiding models of *(40)* do indicate that the amide linkage in the medium-sized ring is somewhat distorted from planarity, thereby causing a reduction in resonance interaction. In tautomer *(41)*, the planar conformation enforced on the β-lactam ring results in restoration of total delocalization and accordant stabilization. Since cyclooctatrienone enjoys no such prerogative, the strain associated with the cyclobutanone ring in the bicyclic form may emerge as the dominant destabilizing factor.

[35] *W. B. Person, G. C. Pimentel,* and *K. S. Pitzer,* J. Amer. Chem. Soc. *74,* 3437 (1952).

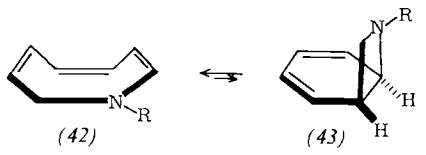
[36] *I. L. Karle,* J. Chem. Phys. *20,* 65 (1952).

[37] *R. Huisgen, F. Mietzsch, G. Boche,* and *H. Seidl:* Organic Reaction Mechanisms, Spec. Publ. Chem. Soc. (London) *19,* 3 (1965).

[38] *L. A. Paquette* and *J. C. Philips,* Chem. Commun. *1969,* 680.

[39] *R. Huisgen, G. Boche, A. Dahmen,* and *W. Hechtl,* Tetrahedron Lett. *1968,* 5215.

Interestingly, sulfonamides *(42a)* and *(42b)* also exist only as azabicyclooctadienes *(43)*[33,34]. Notably, therefore, replacement of the carbonyl function of a dihydroazocinone by a methylene group and the corresponding alteration in the hybridization at that position from sp^2 to sp^3 does not reverse the position of tautomeric

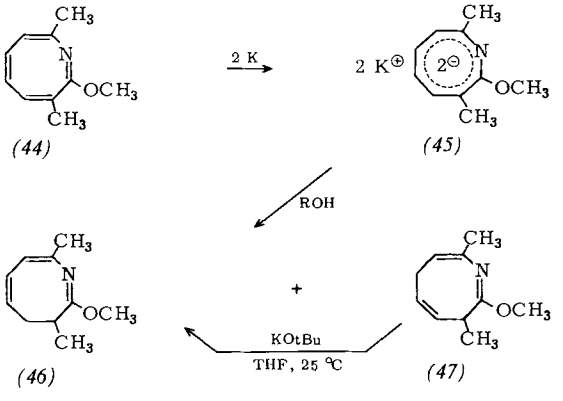


(42) *(43)*

(a), R = $SO_2C_6H_4CH_3$-*p*; *(b)*, R = SO_2CH_3

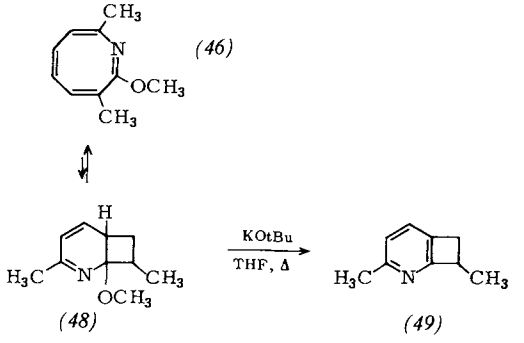
equilibrium. The bicyclic forms may be heavily favored because the appreciably wider bond angles in the four-membered rings lead to a substantial reduction in destabilizing non-bonded interactions. In *(41c)*, this effect would result in relief of the steric interference between *N*-methyl and carbonyl oxygen, whereas in *(43a)* and *(43b)* sulfonyl oxygen/methylene hydrogen interactions would be minimized.

When 2-methoxyazocine *(33)* and a number of its methylated derivatives such as *(44)* are treated with potassium metal in tetrahydrofuran, dimethoxyethane, or liquid ammonia, conversion to the corresponding aromatic 10π-electron dianion [*e.g., (45)*] occurs[40–43]. On protonation with various active hydrogen sources, the formation of 3,4- [*e.g., (46)*] and 3,6-dihydroazocines *(47)* is seen to be preferred. Potassium *tert*-butoxide in



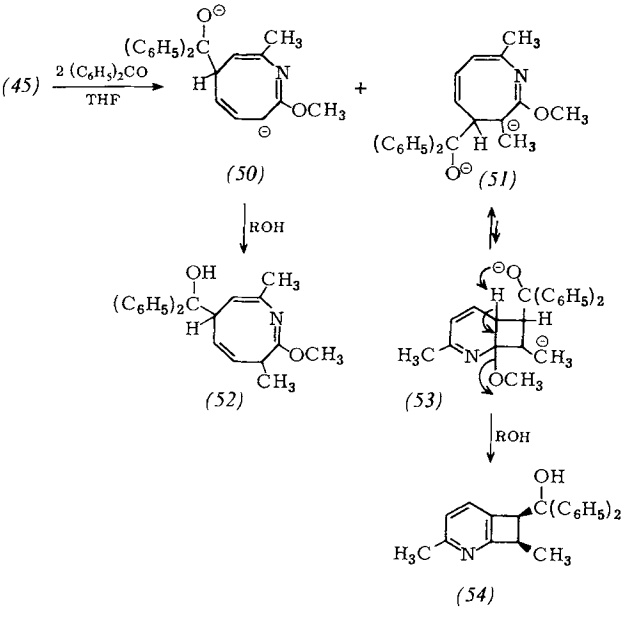
(44) *(45)* *(46)* *(47)*

tetrahydrofuran at room temperature transforms *(47)* into its more extensively conjugated counterpart *(46)* Not unexpectedly, *(46)* does not exhibit a temperature-dependent NMR spectrum; in this instance, valence tautomerism would necessarily lead to *(48)* with attendant disruption of the imino ether function. However, the capability of *(46)* to produce *(48)* in low concentration is revealed by the observation that *(46)* is transformed readily in high yield to cyclobutenopyridine *(49)* when refluxed in tetrahydrofuran solution containing potassium *tert*-butoxide[44]. The passage from *(48)* to *(49)* is undoubtedly assisted by the driving force arising from the incipient aromaticity.



(46) *(48)* *(49)*

Novel intramolecular variants of the above reaction have been uncovered[44]. For example, alkylation of dipotas-



(45) *(50)* *(51)* *(52)* *(53)* *(54)*

sium 3,8-dimethyl-2-methoxyazocinediide *(45)* with two molar equivalents of benzophenone in anhydrous tetrahydrofuran at 25 ° C gives rise to triene *(52)* (1.6%) and 2,3-cyclobutenopyridine *(54)* (46%). The unusual conversion of *(45)* to *(54)* can be rationalized on the premise that alkylation of the azocinyl dianion at C-4 proceeds normally to afford an alkoxide [*e.g., (51)*], followed by valence isomerization of *(51)* to its bicyclic valence tautomer *(53)*, and intramolecular 1,5-proton abstraction with concomitant ejection of methoxide ion and aromatization. This particularly facile synthesis of the previously unknown 2,3-pyridocyclobutene ring system continues to be explored.

5. Azabullvalenes and Benzazabullvalenes

As a consequence of the dynamic fluxional nature of bullvalene *(55)*, all ten constituent carbon atoms find themselves in an ever-changing relationship to each other as

[40] *L. A. Paquette, T. Kakihana,* and *J. F. Hansen,* Tetrahedron Lett. *1970,* 529.

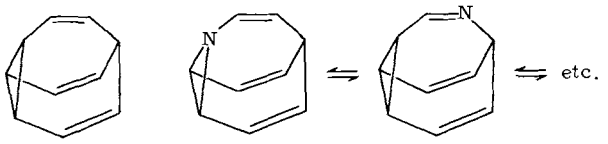
[41] *L. A. Paquette, J. F. Hansen, T. Kakihana,* and *L. B. Anderson,* Tetrahedron Lett. *1970,* 533.

[42] *L. B. Anderson, J. F. Hansen, T. Kakihana,* and *L. A. Paquette,* J. Amer. Chem. Soc., in press.

[43] *L. A. Paquette, J. F. Hansen,* and *T. Kakihana,* J. Amer. Chem. Soc., in press.

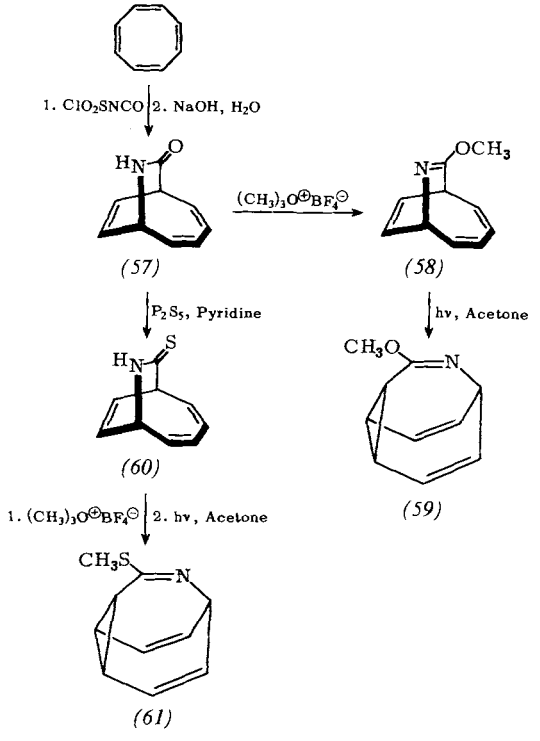
[44] *L. A. Paquette* and *T. Kakihana,* J. Amer. Chem. Soc., in press.

the molecule undergoes interconversion to each of 1,209,600 identical structural arrangements[25,45,46]. *A priori*, azabullvalene *(56)* can be expected to display the same remarkable features as *(55)*, but only if the nitrogen atom is not protected by sufficiently high energy barriers from entering into the various bond reorganizations. In this connection, a remarkably simple synthetic entry into the azabullvalene system has been devised[47–50].



(55) *(56a)* *(56b)*

Thus, cycloaddition of chlorosulfonyl isocyanate to cyclooctatetraene, followed by aqueous hydrolysis, results in 1,4 cycloaddition to the eight-membered ring to afford lactam *(57)*. Acetone-sensitized photoisomerization of the derived imino ether *(58)* leads directly to 2-methoxyazabullvalene *(59)*. The sequenze to methylthioazabullvalene *(61)* proceeds from lactam *(57)* and phosphorus pentasulfide in pyridine through thioamide *(60)* to its thiomethyl imino ether and ultimate photolysis[49].



(57) *(58)* *(60)* *(59)* *(61)*

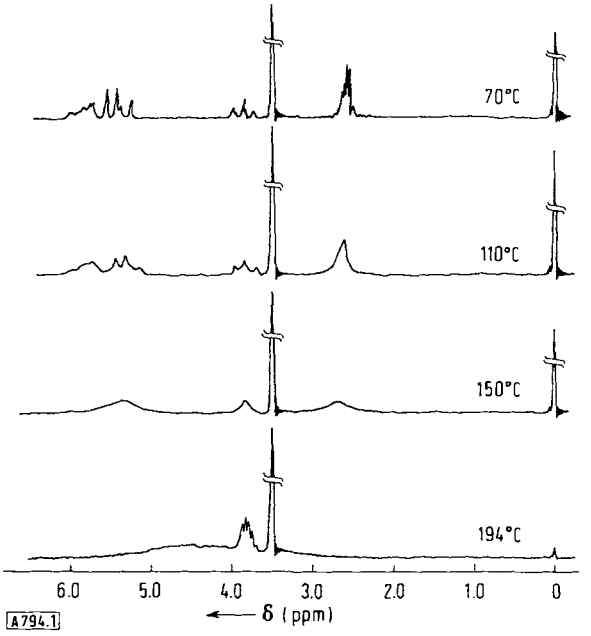


Fig. 1. 60-MHz NMR spectra of *(59)* in $Cl_2C{=}CCl_2$ solution at 70, 110, 150 and 194 °C.

Although the low temperature NMR spectra of *(59)* and *(61)* merely scramble signals within each separate absorption region (indicative of variations in concentration levels of non-degenerate isomers), elevated temperatures cause coalescence of the various proton signals with the exception of the one-proton 3.8–4.1 ppm absorption (the changes are completely reversible). These spectra are reproduced in Figures 1 and 2.

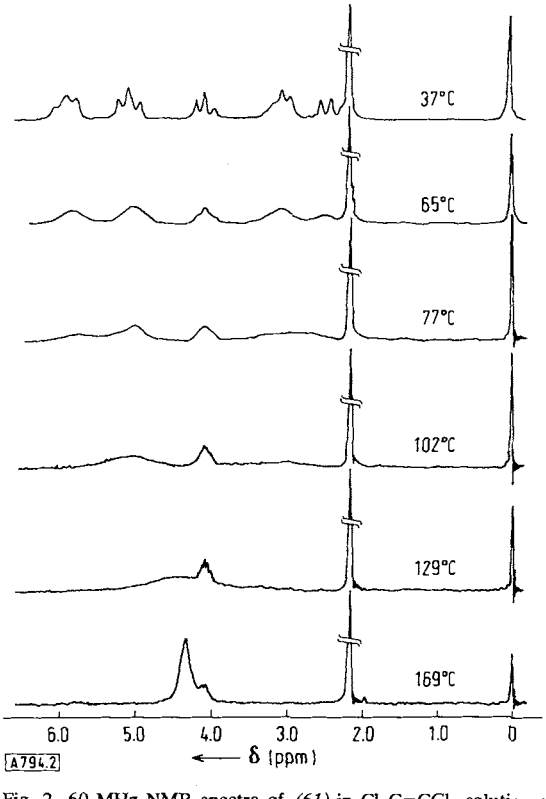


Fig. 2. 60-MHz NMR spectra of *(61)* in $Cl_2C{=}CCl_2$ solution at 37, 65, 77, 102, 129, and 169° C.

[45] *R. Merényi, J.F.M. Oth,* and *G. Schröder,* Chem. Ber. *97,* 3150 (1964).

[46] *W. von E. Doering, B.M. Ferrier, E.T. Fossel, J.H. Hartenstein, M. Jones jr., G. Klumpp, R.M. Rubin,* and *M. Saunders,* Tetrahedron *23,* 3984 (1967).

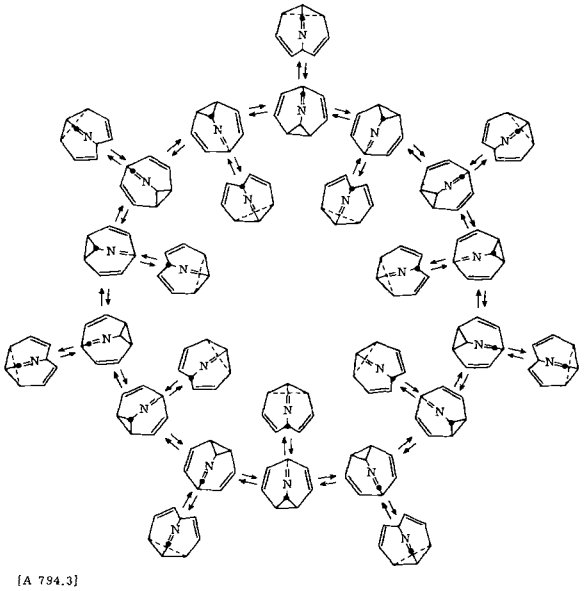
[47] *L.A. Paquette* and *T.J. Barton,* J. Amer. Chem. Soc. *89,* 5480 (1967).

[48] *L.A. Paquette, T.J. Barton,* and *E.B. Whipple,* J. Amer. Chem. Soc. *89,* 5481 (1967).

[49] *L.A. Paquette, J.R. Malpass, G.R. Krow,* and *T.J. Barton,* J. Amer. Chem. Soc. *91,* 5296 (1969).

[50] *L.A. Paquette, J.R. Malpass,* and *T.J. Barton,* J. Amer. Chem. Soc. *91,* 4714 (1969).

Since the ambient temperature spectra reveal the presence of three cyclopropyl and four vinyl protons in addition to the nonexchanging proton, the latter proton must occupy the bridgehead position, there must only be one such proton, and it must be positioned adjacent to nitrogen (chemical shift considerations). The NMR spectra impose the added stringent condition that the favored interconversion routes must preserve the positional integrity of the bridgehead proton and thereby insulate it from the scrambling that occurs among the other protons. The only averaging process that can give rise to the observed behavior is the sequential combination of two Cope rearrangements illustrated in Figure 3. The two-step conversion amounts formally to a rotation of the inner triatomic "spoke" on the outer "rim" by $2\pi/7$ radians (note wheel in Figure 3), it being

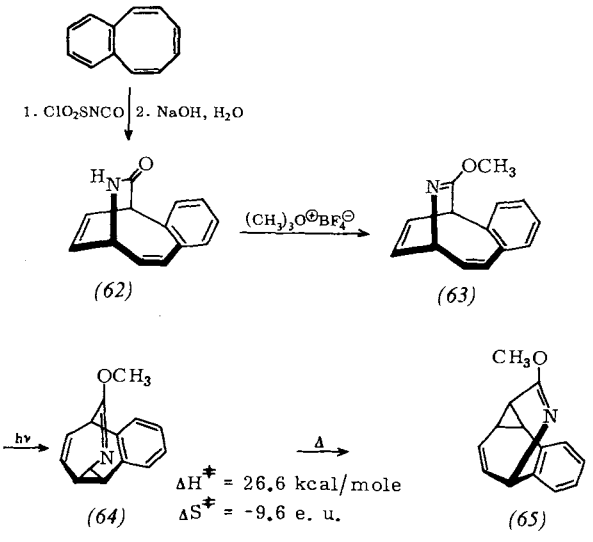


[A 794.3]

Fig. 3. The sequential Cope rearrangements in *(59)* and *(61)* showing the averaging of the seven peripheral hydrogens coupled with retention of the structural integrity of the triatomic "spoke".

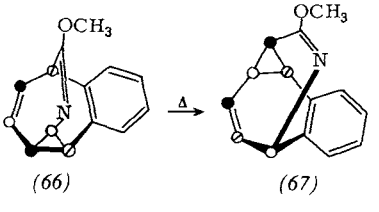
evident that continued repetition of such a process would average the rim positions and exclude the spoke. Each of the seven equivalent structures thus generated is connected by a second Cope rearrangement to a more stable isomer (positioned on the outer periphery of the wheel)[51].

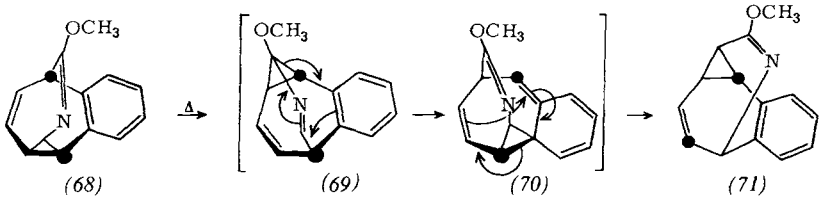
The reason that such a relatively simple averaging process occurs is apparently the strong preference of the nitrogen atom for participation in a double bond. By precluding any rearrangement path that places the heteroatom in the three-membered ring or at the bridgehead position, the integrity of the skeletal atoms constituting



the spoke is maintained and the number of accessible structural arrangements is limited to the 28 shown. The Cope rearrangement which necessitates placement of the methoxyl or methylthio substituent at one of the cyclopropyl positions with simultaneous disruption of the imino ether functionality is very likely rate-determining. The lower coalescence temperature exhibited by *(61)* [relative to *(59)*] denotes that it is somewhat less energetically demanding in the case of $-(CH_3S)C=N-$ than of $-(CH_3O)C=N-$, in agreement with the greater stability of the latter functionality. The decided preference of *(59)* and *(61)* to exist in the ground state as the outermost structures in Figure 3 has been attributed to an electronegativity effect[49].

In contrast, methoxybenzazabullvalene *(64)*, available from benzocyclooctatetraene as shown below, undergoes an irreversible reaction at 125–150 °C with the formation of a different methoxybenzazabullvalene *(65)*[49, 51a].





● = fully deuterated; ∅ = partially deuterated

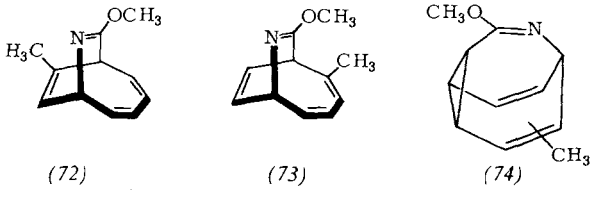
[51] There exists no spectral evidence for the presence of the seven valence tautomers which occupy the inner sphere of the wheel.

[51a] *L. A. Paquette* and *J. R. Malpass*, J. Amer. Chem. Soc. *90*, 7151 (1968).

[52] *L. A. Paquette, J. R. Malpass* and *G. R. Krow*, J. Amer. Chem. Soc. *92*, 1980 (1970).

Appropriate deuterium labeling studies show that the photorearrangement of *(63)* to *(64)* proceeds exclusively by way of a di-π-methane rearrangement involving vinyl-vinyl bonding in its initial stages[52]. More pertinent to the present discussion is the conclusion founded upon the thermal rearrangement of two differently labeled benzazabullvalene A's [*(66)* and *(68)*], that the formation of benzazabullvalene B's *(65)*, *(67)*, and *(71)* is the result of a Cope rearrangement sequence[52]. It is particularly significant and informative that this mechanistic pathway is followed since the first step [*i.e.*, *(68)*→*(69)*] requires disruption of the imino ether functionality, and the second step [*i.e.*, *(69)*→*(70)*] necessitates loss of aromatic character in the benzene ring.

Lastly, consideration should be given to the detailed mechanism which can account for the selectivity in methyl scrambling noted in the pyrolysis of *(72)*-*(74)* (600° C, flow system)[53,54]. Under these conditions, *(72)* and *(73)* suffer loss of methanol and afford in > 95% yield all the possible monomethylquinolines except 2-methylquinoline (Tab. 2). Pyrolysis of *(74)* afforded also a mixture of methylquinolines (95% yield), but in contrast, 2-methylquinoline was now the major product.

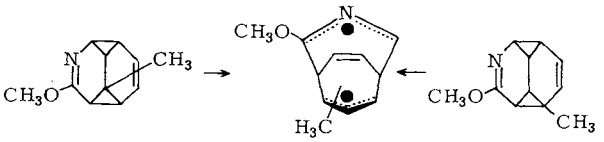


(72) *(73)* *(74)*

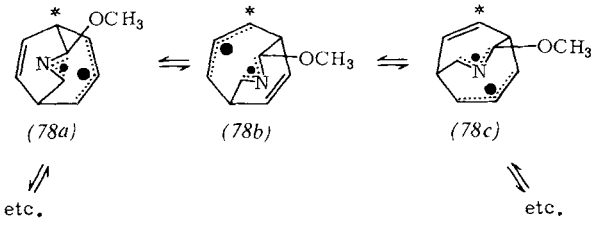
Table 2. Product data for the pyrolysis of *(72)*, *(73)*, and *(74)*.

Products	Substrate pyrolyzed *(72)*	*(73)*	*(74)*
	Composition (%)		
8-Methylquinoline	13	19	11
7-Methylquinoline	25	19	16
6-Methylquinoline	11	17	9
5-Methylquinoline	21	15	12
4-Methylquinoline	25	15	11
3-Methylquinoline	5	15	9
2-Methylquinoline	0	0	32
	100	100	100

It has been proposed[54] that *(72)* and *(73)* first undergo (4+2)π cycloaddition to give the two structurally distinguishable azatetracyclo[4.4.0.0^{2,10}.0^{5,7}]deca-3,8-dienes *(75)* and *(76)*, respectively. Reverse (3+3+2) cycloaddition of these intermediates give the same biradical *(77)*. The most obvious way to preserve the structural integrity of the triatomic nitrogen-containing bridge while allowing for scrambling of the methyl substituent among the remaining seven positions is to invoke a rotation of the heteroatomic bridge about the seven atom rim. In the parent series, this rotation would be totally degenerate [cf *(78)*]; in the case of *(77)*, scrambling of the methyl substituent to all the rim positions occurs with preservation of the absence of alkyl labeling on the carbon atom of the pivoting bridge. Eventually, *(77)* is converted to products by cyclization to *(79)* which aromatizes by ring opening to azacyclodecapentaene *(80)*, recyclization to *(81)*, and ejection of methanol.

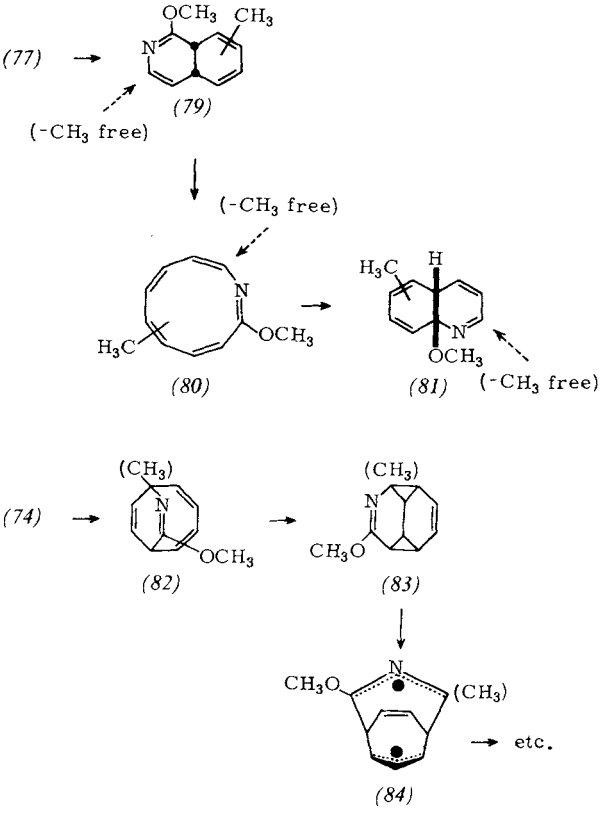


(75) *(77)* *(76)*



(78a) *(78b)* *(78c)*

Azabullvalene *(74)* yields considerable 2-methylquinoline because the methyl substituent has already found its way to the pivoting bridge due to earlier migration. The first step, namely thermal conversion of *(74)* to *(82)* can be experimentally realized at *ca.* 500 °C.



(79) *(80)* *(81)* *(82)* *(83)* *(84)*

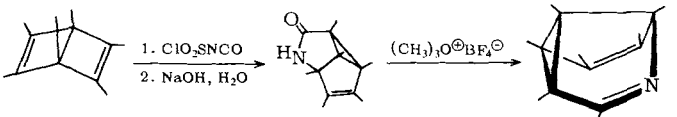
Although the pirouetting effect associated with *(77)* and *(84)* results in a scrambling phenomenon somewhat related to that observed with the azabullvalenes, it is the first example to be encountered in a diradical species.

[53] *L.A. Paquette, G.R. Krow, J.R. Malpass,* and *T.J. Barton,* J. Amer. Chem. Soc. *90*, 3600 (1968).

[54] *L.A. Paquette, G.R. Krow,* and *J.R. Malpass,* J. Amer. Chem. Soc. *91*, 5522 (1969).

6. Azasemibullvalenes

As already noted, the consequence of rigidly locking a divinylcyclopropane moiety into an all-*cis* conformation as, for example, in methoxyazabullvalene is manifested in a marked acceleration of the Cope rearrangement. This fact, and the other considerations developed above, led us to undertake the synthesis of an azasemibullvalene derivative. At issue was the question of whether this ring system would exhibit valence tautomerism.



(85) *(86)* *(87)*

The azasemibullvalene derivative *(87)* has been synthesized in a three-step reaction commencing with hexamethyl (Dewar benzene) *(85)*[55,56]. Treatment of *(85)* with chlorosulfonyl isocyanate in cold methylene chloride solution and subsequent mild hydrolysis affords lactam *(86)* in excellent (87%) yield. *O*-Methylation of *(86)* with trimethyloxonium fluoroborate readily gave *(87)*. The NMR spectrum of *(87)* remained unaltered from $-40°$ to $+150°C$. Clearly, therefore, the restrictions imposed by the imino ether grouping on the possible Cope rearrangement parallel those observed with methoxyazabullvalene.

We wish to express our appreciation to the National Science Foundation, the National Institutes of Health, and Eli Lilly and Company for their support of the work performed at The Ohio State University in cooperation with my most able colleagues Larry Anderson, James Barrett, Thomas Barton, Robert Haluska, John Hansen, Tsuyoshi Kakihana, John Kelly, Grant Krow, Donald Kuhla, Louis Leichter, John Malpass, J. Christopher Philips, and Earl Whipple.

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German version: Angew. Chem. *83*, 11 (1971)

[55] *L.A. Paquette*, Tetrahedron Lett. *1968*, 2133.

[56] *L.A. Paquette* and *G.R. Krow*, J. Amer. Chem. Soc. *91*, 6107 (1969).

Progress in the Hetaryne Field[1]

By Thomas Kauffmann and Rolf Wirthwein[*]

Dedicated to Professor Wilhelm Klemm on the occasion of his 75th birthday

During recent years, instead of concentrating on the detection of the intermediacy of new hetarynes, as they did between 1958 and 1964, workers in this field have been more concerned with the critical sifting and checking of the earlier work. Special interest has been shown in the relation between structure and reactivity in the hetarynes. It has been shown that in addition to the elimination-addition mechanism (EA; hetaryne intermediate), other reaction paths (anomalous addition-elimination mechanism [AE_a] and "Reinecke mechanism") are possible for nucleophilic cine-substitutions on hetaryl halides. The use of deuterated hetaryl halides has proved very valuable for the elucidation of the mechanism of nucleophilic substitutions. Even where substitution mechanisms are superimposed on one another the occurrence of a hetaryne intermediate can be detected by a technique known as the "base competition method". A five-membered hetaryne (4,5-didehydro-1-methylimidazole) has been detected for the first time by this method with a probability that borders on certainty. Selectivity determinations have shown that the replacement of a CH group in 1,2-didehydrobenzene and in 1,2-didehydronaphthalene by an N atom distinctly increases the reactivity to bases. According to EHT (Extended Hückel Theory) calculations, the as yet hypothetical 2,3-didehydropyridine is richer in energy than 3,4-didehydropyridine; this agrees more closely with the experimental findings than the opposite result obtained from simple MO calculations. Besides cine-substitution (1,2 shift), tele-substitution (1,3-shift) has also been observed on reaction of hetaryl halides (pyridine, quinoline, and pyrimidine systems) with bases. An EA mechanism (via m-didehydrohetarenes) and an AE_a mechanism are considered as alternatives for the tele-substitution.

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[1] Hetarynes, Part 15. – Part 14, see ref. [15].

1. Introduction

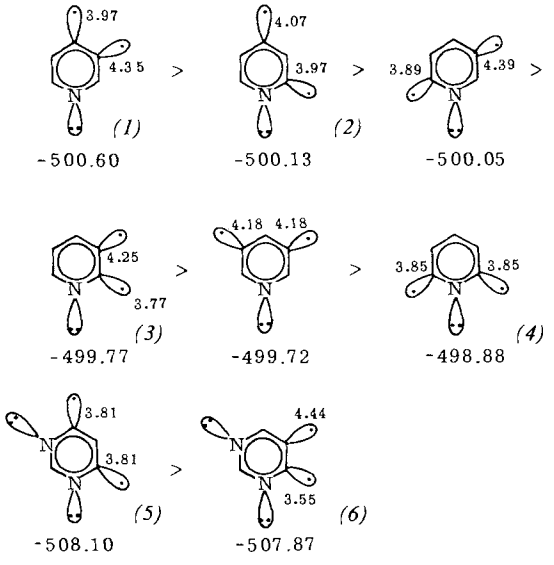
Hetaryne chemistry, which developed rapidly after the discovery of 3,4-didehydropyridine (1959–1961) has already been the subject of four reviews covering the entire field [2–4]; nevertheless, the present article seems justified by new important findings. It also reports hitherto unpublished results obtained in our own research group by the base competition method. Five-membered hetarynes containing one hetero atom will be dealt with in least detail, since the latest position of investigations in this field has been adequately summarized in the two most recent reviews [2b, 4].

2. Six-Membered Hetarynes

2.1. EHT Calculations

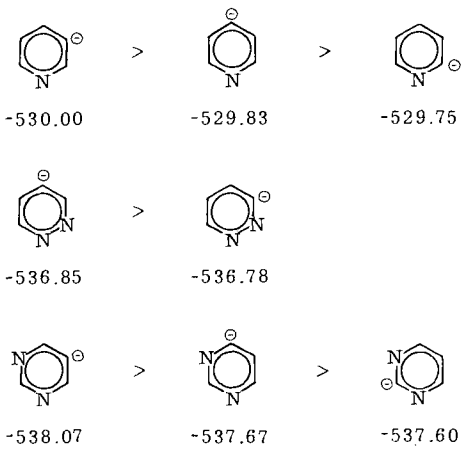
R. Hoffmann et al. [5] have carried out EHT calculations for six-membered didehydrohetarenes and for deprotonated six-membered hetarenes, which may be taken as models for anionic didehydrohetarene precursors. The results (Tables 1 and 2) lead to a better understanding of earlier experimental observations, and will therefore be presented first.

Table 1. Total energies in eV (figures under the formulas) [6] and total valence electron densities (figures beside the orbitals) of the didehydropyridines *(1)–(4)* and of 4,5- and 4,6-didehydropyrimidines *(6)* and *(5)* [5].



Whereas simple Hückel calculations (MO theory)[7] indicated that the o-didehydropyridine *(1)* is richer in energy than *(3)*, EHT calculations lead to the opposite result. The hypothetical 2,6-didehydropyridine *(4)*, to which a relatively high stability was formerly ascribed because of the possibility of delocalization of the electrons of the extra orbitals over three atoms[7], is the least stable of all the possible didehydropyridines according to the EHT calculations, and 2,4-didehydropyridine *(2)*, whose 6-ethoxy derivative has recently been considered as an intermediate in a tele-substitution[8] (cf. Section 4), is situated even higher than 2,3-didehydropyridine *(3)* on the stability scale.

Table 2. Total energies of hetarene anions [5] in eV [6].



A higher stability is now also predicted for 4,6-didehydropyrimidine *(5)* than for 4,5-didehydropyrimidine *(6)*. On the whole, the EHT calculations contradict the previously assumed[7] stabilization by delocalization of the extra electrons over three adjacent ring atoms, and indicate, on the contrary, that pronounced destabilization of a didehydrohetarene results if the orbital of the lone pair of electrons of an N atom is immediately adjacent to the extra orbitals of the aryne bond (cf. also[9]).

Similarly, the lone pair of electrons of a nitrogen atom appears to have a destabilizing influence on *anions of six-membered hetarenes* if the anionized C atom is adjacent to the N atom (cf. Table 2).

The calculated stability sequences and total valence electron densities are in good agreement with experimental observations. For example, they explain why the action of strong bases on 3-halogenopyridines leads only to 3- and 4-substituted, but not to 2-substituted pyridines[2,3], since it must be assumed from Tables 2 and 1 that the intermediate anion *(7)* is poorer in energy than *(8)*, and that the hetaryne *(1)* is poorer in energy (by 0.83 eV or 19 kcal/mole) than *(3)*. The calculated values agree with the fact that the base-catalyzed H/D exchange in 3-chloropyridine takes place much more easily in position 4 than in position 2[10].

[2] a) *H. J. den Hertog* and *H. C. van der Plas*, Advan. Heterocycl. Chem. *4*, 121 (1965); b) *H. J. den Hertog* and *H. C. van der Plas* in *H. G. Viehe:* Chemistry of Acetylenes. M. Dekker, New York 1969, p. 1149.

[3] *Th. Kauffmann*, Angew. Chem. *77*, 557 (1965); Angew. Chem. internat. Edit. *4*, 543 (1965).

[4] *R. W. Hoffmann:* Dehydrobenzene and Cycloalkynes. Verlag Chemie, Weinheim and Academic Press, New York 1967, p. 275.

[5] *W. Adam, A. Grimison*, and *R. Hoffmann*, J. Amer. Chem. Soc. *91*, 2590 (1969); the total valence electron density on the atoms of the extra bond in 1,2-didehydrobenzene was found to be 4.20.

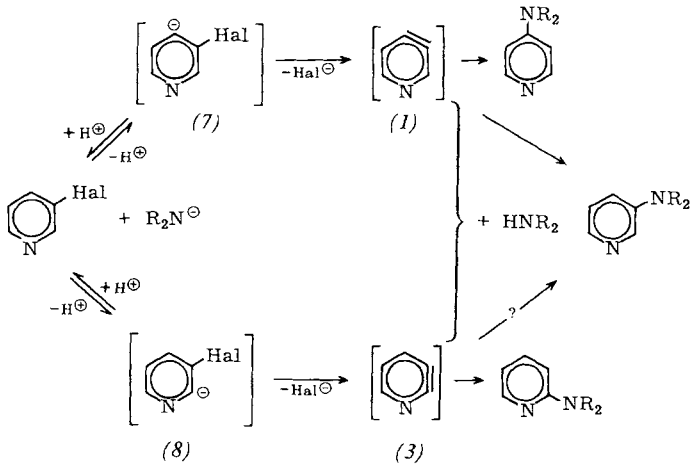
[6] The values for the total energy are comparable only within the group of compounds having the same number of nitrogen atoms. Of the compounds in Table 1, only *(1)* and *(6)* have been definitely detected.

[7] *H. L. Jones* and *D. L. Beveridge*, Tetrahedron Lett. *1964*, 1577.

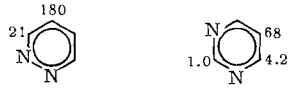
[8] *H. Boer* and *H. J. den Hertog*, Tetrahedron Lett. *1969*, 1943.

[9] *R. A. Abramovitch, G. M. Singer*, and *A. R. Vinutha*, Chem. Commun. *1967*, 55.

[10] *J. A. Zoltewicz* and *C. L. Smith*, J. Amer. Chem. Soc. *88*, 4766 (1966); *89*, 3358 (1967).



The results of EHT calculations for the anions of diazines (Table 2), which may also be taken as models for anionic hetaryne precursors, again agree with experimental findings since the following relative rates were found in H/D exchange studies (in *O*-deuteriomethanol at 165 °C)[11]:



Further criteria are provided by the orientation phenomena in the addition of nucleophiles to hetarynes. It can be assumed from the calculated electron densities (Table 1) that a nucleophilic attack on 3,4-didehydropyridine will take place preferentially in position 4. Ammonia[2] and (much less definitely) secondary amines[12, 14b] are in fact added preferentially in position 4. Similarly, in the addition of amines to 3,4-didehydroquinoline *(9)* (in comparison with 1,2-didehydronaphthalene), the α-C atom of the extra bond (C-4) is distinctly favored over the β-C atom (C-3) (cf. Table 5), again in agreement with the results of the EHT calculations[5].

Finally, according to the EHT calculations, 2,3-didehydropyridine *(3)* and 4,5-didehydropyrimidine *(6)* should add nucleophiles preferentially in positions 2 and 4 respectively. Though nothing certain is known as yet about the regiospecificity of the addition of bases to *(3)* and *(6)*, there is considerable evidence (cf. Sections 2.3.3 and 2.4) to suggest that these predictions are correct. It will merely be mentioned that SCF (self-consistent field) calculations for hetarynes[13] show that the ground state of these molecules is a singlet state.

2.2. Selectivity Toward Bases

Extensive studies have been devoted to the question how hetero atoms influence the reactivity of the arynes[14, 15]. These investigations have been carried out by competition experiments such as were used earlier by *Huisgen et al.*[16] to compare the reactivities of 1,2-didehydrobenzene, 1,2-didehydronaphthalene, and 9,10-didehydrophenanthrene.

The competition constants found in these earlier measurements with the base pair phenyllithium/lithium piperidide for the carbocyclic arynes mentioned were $K = 4.4$, 5.8, and 12.8, respectively. On the basis of bond lengths of 1.39 Å for the CC bond in benzene (X-ray analysis), 1.365 Å for the 1,2 bond in naphthalene (X-ray analysis), and 1.352 Å for the 9,10 bond in phenanthrene (calculated value)[17], it was concluded that the increasing selectivity and decreasing reactivity indicated by the competition constants were due to increasing overlap of the extra orbitals in the order 1,2-didehydrobenzene, 1,2-didehydronaphthalene, 9,10-didehydrophenanthrene[16].

2.2.1. Competition Constants

The base pair phenyllithium/lithium piperidide used in competition experiments with carbocyclic arynes[16] is unsuitable for use with hetarynes such as 3,4-didehydropyridine or 5,6-didehydroquinoline, since undesirable side reactions[3] occur. Diethylamine and diisopropylamine were therefore used as the base pair for the competition experiments with hetarynes, in which only aryl halides were used that react entirely by the EA mechanism under the reaction conditions (for detection cf.[15]).

To produce the aryne, a solution of phenyllithium in ether is added dropwise to a solution of an aryl halide and the two amines (used in various proportions) in ether (molar ratio aryl halide : phenyllithium : Σ amines = 1 : 1 : 10). The amines are metalated by the phenyllithium to form lithium amides. These convert the aryl halide into the aryne and are themselves continuously consumed, so that their concentration is always low in relation to the concentration of the amine. Check experiments[15] have confirmed that essentially only the free amines are added to the aryne intermediates.

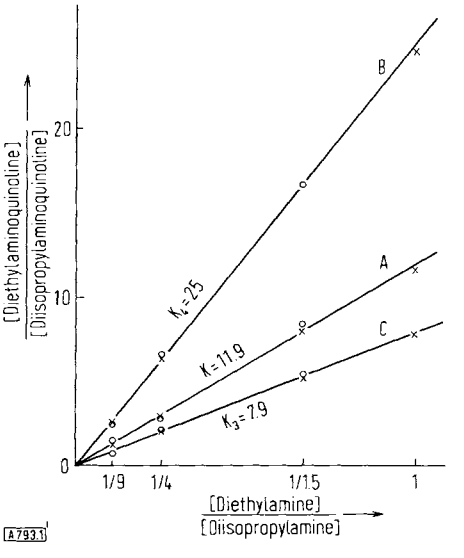


Fig. 1. Determination of the competition constant K (line A) and of the partial competition constants K_3 (line C) and K_4 (line B) in the competitive addition of diethylamine/diisopropylamine to 3,4-didehydroquinoline [25, 26]. O: starting compound 3-chloroquinoline; ×: starting compound 3-bromoquinoline.

When the ratio of the quantities of substitution products, *e.g.* the compounds *(10)*–*(13)* in the reaction of 3-halogenoquinolines, as found by gas chromatography, was plotted against the ratio of diethylamine to diisopropyl-

[11] *J. A. Zoltewicz* and *G. Grahe*, Abstracts, 155th National Meeting Amer. Chem. Soc., San Francisco, Calif., April 1968, p. 128; cited in ref. [5].

[12] *Th. Kauffmann* and *F. P. Boettcher*, Chem. Ber. *95*, 1528 (1962).

[13] *T. Yonezawa, H. Konishi*, and *H. Kato*, Bull. Chem. Soc. Jap. *41*, 1031 (1968).

[14] a) *Th. Kauffmann, H. Fischer, R. Nürnberg, M. Vestweber*, and *R. Wirthwein*, Tetrahedron Lett. *1967*, 2911; b) *1967*, 2917.

[15] *Th. Kauffmann, H. Fischer, R. Nürnberg*, and *R. Wirthwein*, Liebigs Ann. Chem. *731*, 23 (1970).

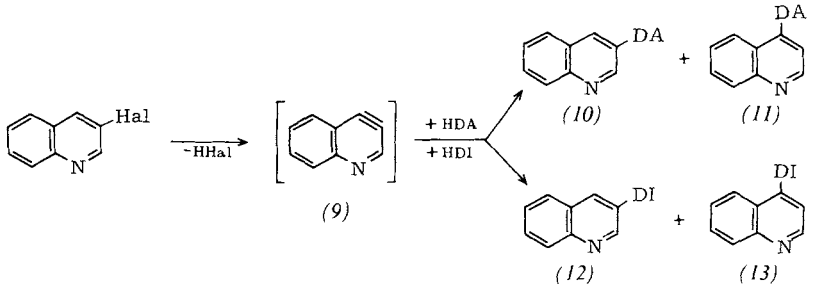
[16] *R. Huisgen, W. Mack*, and *L. Möbius*, Tetrahedron *9*, 29 (1960).

[17] *J. Trotter*, Acta Crystallogr. *16*, 605 (1963), has since then found a value of 1.372 Å by X-ray analysis.

amine, the result was a straight line (*e.g.* A in Fig. 1), the slope of which corresponds to the competition constant:

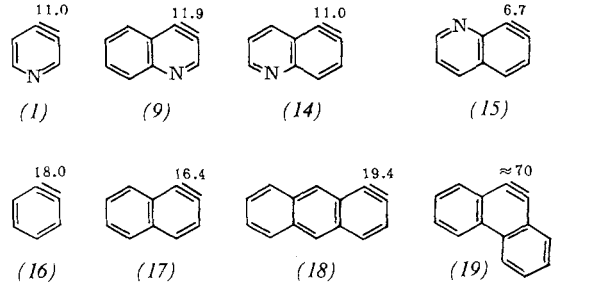
$$K = \frac{[\text{diethylaminoarenes}]}{[\text{diisopropylaminoarenes}]} \times \frac{[\text{diisopropylamine}]}{[\text{diethylamine}]}$$

of the aryne. Competition constants found in this way are given in Table 3.



Hal = Cl, Br; DA = $N(C_2H_5)_2$; DI = $N(i\text{-}C_3H_7)_2$

Table 3. Competition constants in competition experiments with diethylamine/diisopropylamine.



The competition constants show the following:

1) The replacement of a CH group that is not adjacent to the extra bond in 1,2-didehydrobenzene or 1,2-didehydronaphthalene by a nitrogen atom considerably decreases the selectivity toward bases[18], since additions to the hetarynes *(1)*, *(9)*, and *(15)* are much less selective than additions to the corresponding carbocyclic arynes *(16)* and *(17)*. Since the presence of nitrogen as a hetero atom in aromatic systems results in a system having fewer π electrons, the increased electrophilic activity of hetarynes is understandable.

2) Fusion of a benzene or pyridine ring onto the 3,4-bond of 1,2-didehydrobenzene also leads to a decrease in selectivity.

3) In agreement with *Huisgen*'s results[16], fusion of a benzene ring onto 1,2-didehydrobenzene on each side of the extra bond [9,10-didehydrophenanthrene *(19)*] greatly increases the selectivity.

2.2.2. Partial Competition Constants

A base normally adds to an aryne in both possible orientations. In an aryne that is unsymmetrical with respect to the extra bond (as is normal in heterocyclic arynes), therefore, it is possible to distinguish two addition reactions, *e.g.* addition of the base residue to C-3 and C-4 in 3,4-didehydroquinoline *(9)*. In competition experiments (cf. Section 2.2.1), therefore besides the competition constant K, which refers to both orientations of the addition of the base (line A in Fig. 1), one can also determine "partial competition constants" (K_1, K_2, K_3, *etc.*) for the two partial reactions[14b, 15], which are defined in the same way as K (lines B and C in Fig. 1). For 3,4-didehydroquinoline *(9)* and the base pair diethylamine/diisopropylamine, for example,

$$K_3 = \frac{[\text{3-diethylaminoquinoline}]}{[\text{3-diisopropylaminoquinoline}]} \times \frac{[\text{diisopropylamine}]}{[\text{diethylamine}]}$$

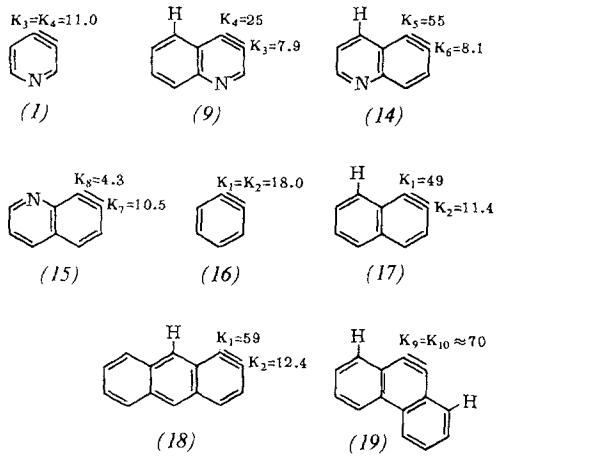
$$K_4 = \frac{[\text{4-diethylaminoquinoline}]}{[\text{4-diisopropylaminoquinoline}]} \times \frac{[\text{diisopropylamine}]}{[\text{diethylamine}]}$$

The partial competition constants (Table 4) show the selectivity at the two C atoms of the extra bond, and are therefore often more informative than the competition constants K. In unsymmetrical arynes whose extra bond is in the α,β position in relation to a fused aromatic ring, the α-C atom of the extra bond exhibits a particularly high partial competition constant, *i.e.* the system has a high "α-selectivity", if there is an H atom in the peri position with respect to the α-C [arynes *(9)*, *(14)*, *(17)*, and *(18)*]. This may be assumed to be partly or entirely due to steric hindrance of the addition of diisopropylamine. Thus steric hindrance of the addition of the bulky diisopropylamine to the α-C atom because of the H atom in the peri position has been found for 1,2-didehydronaphthalene *(17)*[19], 3,4-didehydroquinoline *(9)*, and 5,6-didehydroquinoline *(14)*[15], whereas the addition of diethylamine is unhindered (cf. Table 5). The extremely low α-selectivity of 7,8-didehydroquinoline *(15)*, in which there is no steric hindrance to the addition to the α-C atom, because of the absence of an H atom in the peri position, is further evidence that steric hindrance is a cause of high α-selectivity. In this case the β (7) position should be more strongly screened than the α (8) position, since the orbital of a lone pair of electrons on the nitrogen should take up less space than an H atom (cf. Table 5).

[18] *Kauffmann* and *Nürnberg* [3], on the other hand, found a higher selectivity for 3,4-didehydropyridine ($K = 1.5$) than for 1,2-didehydrobenzene ($K = 1.0$) in competition experiments with piperidine/diethylamine. Later investigations showed, however, that the results of competition experiments with this base pair are not very conclusive; cf. [14, 15].

[19] *R. Huisgen* and *L. Zirngibl*, Chem. Ber. *91*, 2375 (1958).

Table. 4. Partial competition constants in competition experiments with diethylamine/diisopropylamine.



The extremely high selectivity of 9,10-didehydrophenanthrene *(19)* is evidently due to the fact that double the "α-selectivity" is found in this case since the C atoms of the extra bond both correspond to the α-C atom of *(17)* as far as the neighborhood of a peri-H atom is concerned[20].

Table 5. Addition of the base residue to the two C atoms of the extra bond in the addition of bases to 1,2-didehydronaphthalene and aza analogs.

Aryne	Reaction with	Addition (%) to C-α[a]	to C-β[a]	Ref.
1,2-didehydronaphthalene *(17)*	piperidine	31	69	[22]
	diethylamine	39	61	[22,15]
	diisopropylamine	13	87	[19,15]
	dicyclohexylamine	7	93	[19]
	phenyllithium	36	64	[23]
	lithium piperidide	25	75	[15]
3,4-didehydroquinoline *(9)*	piperidine	51	49	[24]
	diethylamine	51	49	[14b,25]
	diisopropylamine	25	75	[14b,25]
	dicyclohexylamine	27	73	[26]
	KNH_2/NH_3	56	44	[27]
5,6-didehydroquinoline *(14)*	piperidine	28	72	[28]
	diethylamine	31	69	[14b,15]
	diisopropylamine	5-6	94-95	[14b,15]
7,8-didehydroquinoline *(15)*	piperidine	36	64	[15]
	diethylamine	40	60	[15]
	diisopropylamine	62	38	[15]

[a] Based on the undehydrogenated aromatic nucleus.

[20] Steric hindrance is presumably also responsible for the high selectivity of 9,10-didehydrophenanthrene in the competitive addition of phenyllithium and lithium piperidide [16] (both are dimeric in ether [21]), since lithium piperidide is added to a smaller extent than phenyllithium in the sterically hindered α position of 1,2-didehydronaphthalene (cf. Table 5).

[21] *G. Wittig, F. J. Meyer,* and *G. Lange,* Liebigs Ann. Chem. *571,*167 (1951); *R. Huisgen, H. König,* and *N. Bleeker,* Chem. Ber. *92,* 424 (1959).

[22] *J. Sauer, R. Huisgen,* and *A. Hauser,* Chem. Ber. *91,* 1461 (1958).

[23] *R. Huisgen* and *L. Zirngibl,* Chem. Ber. *91,* 1438 (1958).

[24] *Th. Kauffmann, F.-P. Boettcher,* and *J. Hansen,* Liebigs Ann. Chem. *659,* 102 (1962).

[25] *Th. Kauffmann, R. Nürnberg,* and *R. Wirthwein,* Chem. Ber. *102,* 1161 (1969).

[26] *R. Wirthwein,* Dissertation, Technische Hochschule Darmstadt 1969.

In the bicyclic arynes *(9), (14),* and *(17),* as well as in *(18),* on the other hand, the high α-selectivity is less noticeable in the overall behavior of the arynes, since it is offset by the lower selectivity of the β-C atom. This "β-selectivity" is much more strongly dependent on electronic factors than the α-selectivity, and so provides more information about effects of that kind (cf.[15]). The overall impression conveyed by the data in Tables 3 and 4 is that, apart from steric factors, *the situation in the arynes is similar to that in the corresponding arenes;* in both cases the reactivity toward bases is increased by replacement of ring C atoms by N atoms and by fusion of aromatic rings.

2.3. EA/AE_n Competition in Nucleophilic Substitutions on Hetaryl Halides

Since there is as yet no method by which hetarynes can be produced in reasonable quantities, except by the action of bases on hetaryl halides, the main importance of the hetarynes still lies in their occurrence as intermediates in nucleophilic substitutions on hetaryl halides by the EA mechanism. In these reactions, the substitution by the EA mechanism is frequently (much more so than in the carbocyclic series) accompanied by substitution by the normal addition-elimination (AE_n) mechanism. This is often an undesirable situation from the preparative point of view, but the EA or the AE_n mechanism can be favored as desired by suitable choice of the conditions.

2.3.1. Factors that Determine the EA/AE_n Ratio

Whereas earlier investigations on EA/AE_n competition in the action of bases on halides of six-membered hetarenes had yielded abundant information (cf. "Mechanism Maps"[3]) about the influence of the proton affinity of the nucleophile (lithium amide and free amines) and the position of the halogen on the aromatic system, the topics studied in recent years have been the effects of the bulkiness of the nucleophile and of the nature of the halogen[29]. Investigations of this nature were possible for 4-halogenopyridines following the discovery, in reactions of 3-halogenopyridines (Cl, Br) in boiling ether with lithium piperidide/piperidine[12], lithium diethylamide/diethylamine[29], and lithium diisopropylamide/diisopropylamine[29], that 3,4-didehydropyridine formed as an intermediate under these conditions reacts in a constant "aryne ratio" of 48:52 to form the 3- and 4-substituted pyridines[30].

The same substitution products were formed in similar reactions with 4-chloropyridine. However, the aryne ratio of about 48:52 was found only when the very bulky

[27] *H. J. den Hertog* and *D. J. Buurman,* Recl. Trav. Chim. Pays-Bas *86,* 187 (1967).

[28] *Th. Kauffmann, J. Hansen,* and *R. Wirthwein,* Liebigs Ann. Chem. *680,* 31 (1964).

[29] *Th. Kauffmann* and *R. Nürnberg,* Chem. Ber. *100,* 3427 (1967).

[30] There is very much more free amine than lithium amide present under the experimental conditions. The hetaryne thus probably reacts almost exclusively with the free amine [20].

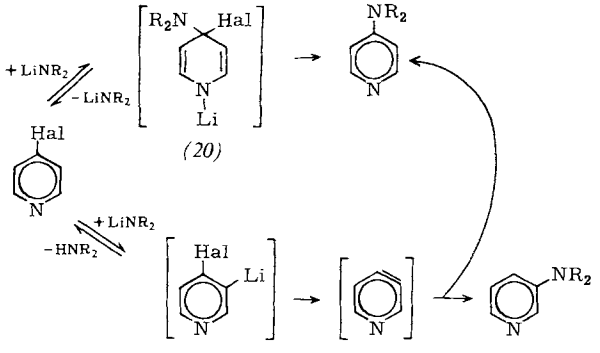
lithium diisopropylamide was used[29]. With the other lithium amides, the increased formation of the 4-isomer (cf. Table 6) showed the participation of the AE_n mechanism. With lithium piperidide as the base, the AE_n mechanism almost completely displaced the EA mechanism. Table 6 shows similar situations in corresponding reactions with 4-chloroquinoline, 3-fluoroquinoline, and 8-chloroquinoline.

Table 6. Influence of the bulkiness of the nucleophile on the mechanism of nucleophilic substitutions on hetaryl halides (in ether, 35 °C).

Hetaryl halide	Base [a]	AE_n (%)	EA (%)
4-chloropyridine [29]	LiPip/HPip	97	3
	LiDA/HDA	19	81
	LiDI/HDI	0	100
4-chloroquinoline [26]	LiPip/HPip	91	9
	LiDA/HDA	20	80
	LiDI/HDI	0	100
3-fluoroquinoline [26]	LiPip/HPip	100	0
	LiDA/HDA	12	88
	LiDI/HDI	0	100
8-chloroquinoline [26]	LiPip/HPip	98	2
	LiDA/HDA	65	35
	LiDI/HDI	no substitution reaction	

[a] Pip, DA, DI = piperidino, diethylamino, and diisopropylamino residues.

The increasing participation of the AE_n mechanism in the order lithium diisopropylamide < diethylamide < piperidide can be best explained by the assumption that with decreasing bulkiness the amines react more rapidly with the hetaryl halides listed in Table 6 to form an adduct of the type *(20)*. In the EA mechanism, which begins with *o*-metalation of the halide, the bulkiness of the base, as expected, is less important.



The dependence of the EA/AE_n ratio on the nature of the halogen had been recognized in reactions of 3-halogenopyridines[12] with lithium piperidide/piperidine, since the fluoro compound, unlike the other 3-halogenopyridines, reacted exclusively by the AE_n mechanism. The reactions listed in Table 7 for 4-halogenopyridines and 4-halogenoquinolines show that even the replacement of chlorine by bromine can have a decisive effect on the EA/AE_n ratio.

Since less bulky base residues favor the AE_n mechanism in relation to the EA mechanism, it seems reasonable to attribute the increasing participation of the AE_n mechanism in the order I < Br < Cl < F to the decreasing bulk of the halogens, since the adduct formation is increasingly facilitated. However, other explanations are also offered by the difference in the polarizabilities of the halogen atoms[29].

Table 7. Influence of the halogen in hetaryl halides on the mechanism of the nucleophilic aromatic substitution (in ether, 35 °C).

Base	Hetaryl halide	AE_n (%)	EA (%)	Ref.
LiPip/HPip	4-fluoropyridine	100	0	[29]
LiPip/HPip	4-chloropyridine	97	3	[29]
LiPip/HPip	4-bromopyridine	10	90	[29]
LiPip/HPip	4-iodopyridine	4	96	[29]
LiPip/HPip	4-chloroquinoline	91	9	[26]
LiPip/HPip	4-bromoquinoline	16	84	[26]
LiDA/HDA	4-chloropyridine	19	81	[29]
LiDA/HDA	4-bromopyridine	0	100	[29]

[a] Pip, DA = piperidino and diethylamino residues.

If it is desired to avoid the EA mechanism, which generally leads to an isomer mixture, it is therefore advisable to use less bulky bases and a fluoro or chloro compound of the hetarene in question. If, on the other hand, one wishes the formation of a hetaryne, *i.e.* if one wishes to promote the EA mechanism, relatively bulky bases should be allowed to react with the appropriate bromide or iodide; however, reductive dehalogenation tends to occur as a side reaction when bromides are used, and this tendency is further increased with iodides.

2.3.2. Detection of Hetarynes when EA and AE_n Mechanisms Occur Concurrently ("Base Competition Method")

The carbocyclic or heterocyclic aryne formed in the EA mechanism usually adds bases in both possible orientations. Where an unsymmetrical aryne intermediate occurs, therefore, an "unrearranged" substitution product and a "rearranged" product are normally formed. In a pure EA mechanism, the ratio of these products is determined only by the rates of addition of the base to the aryne in the two orientations. The occurrence of an aryne intermediate and reaction exclusively by the EA mechanism can therefore be conclusively demonstrated if the isomer ratio can be shown to be constant when the halogen in the starting compound is varied[31]. The validity of this method depends on two conditions:

1) Two substitution products must be formed.

2) No other mechanism of nucleophilic aromatic substitution may occur in addition to the EA mechanism.

If one of these two conditions is not satisfied (superposition of two or three mechanisms of nucleophilic aromatic substitution is shown, if two substitution products are formed, by the inconstancy of the isomer ratio when the halogen is varied), the "base competition method"[25,32] may be used for the detection of arynes (only with reservations where three mechanisms occur). This is particularly important in the heterocyclic series, since an additive mechanism is then often superimposed

[31] *R. Huisgen* and *J. Sauer*, Chem. Ber. *91*, 1453 (1958).

[32] *Th. Kauffmann, R. Nürnberg, J. Schulz*, and *R. Stabba*, Tetrahedron Lett. *1967*, 4273.

on the EA mechanism; moreover, the detection of heterocyclic arynes by interception with dienes has proved very unreliable[4,33].

In the "base competition method", two aryl halides that differ only in the nature of the halogen atom are allowed, in separate experiments, to react with *two* bases (competition experiments, cf. Section 2.2). The molar ratios of the "unrearranged" and/or "rearranged" substitution products as found by gas chromatography are plotted on graphs against the molar ratio of the competing bases. It is generally possible to recognize, from the resulting diagram, which substitution mechanisms (EA, AE_n, AE_a) occur.

If the aryl halides are sufficiently reactive to react with free secondary amines, the competition experiments are carried out in an autoclave at 130–180 °C without the addition of phenyllithium (method A). For less reactive halides, phenyllithium is added (method B), as described in connection with the selectivity determinations (cf. Section 2.2).

The "base competition method" derives from the fact that in a pure AE_n mechanism the competition constants found in the competition experiments are distinctly dependent on the halogen of the starting compound (cf. Fig. 2), whereas no dependence on the halogen is found in a pure EA mechanism (cf. Fig. 1), since the competition constants in this case are determined only by the rates at which the competing bases add to the common halogen-free aryne intermediate. This characteristic of the EA mechanism is also valid for the partial competition experiments (cf. Fig. 1); it can therefore be used for the detection of the EA mechanism in cases of EA/AE_n (or EA/AE_a) superposition, since only one of the two[34] partial competition constants determined by the EA mechanism will be affected by the superposition.

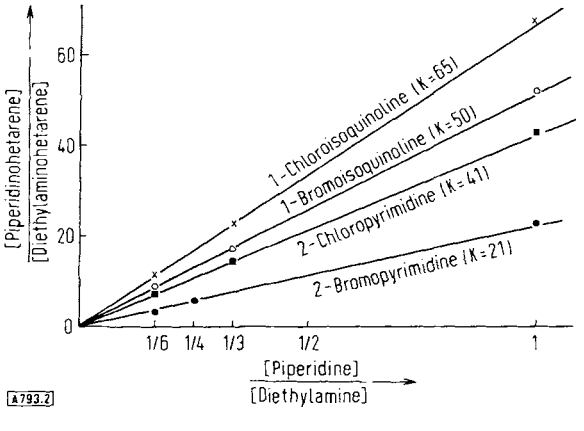
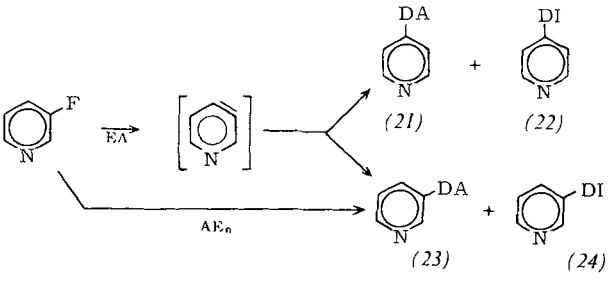


Fig. 2. Dependence of the competition constant on the halogen in nucleophilic substitution reactions with a pure AE_n mechanism. Reaction with piperidine/diethylamine (2-halogenopyrimidines by method A, 1-halogenoisoquinolines by method B). Since there is no H atom *o* to the halogen, the EA mechanism *via* a hetaryne intermediate is impossible here.

This can be illustrated by a concrete example. In competition experiments with diethylamine/diisopropylamine (by method B), 3-fluoropyridine reacts partly by the EA mechanism and partly by the AE_n mechanism, as is shown by the ratio of the 3- and 4-substitution products (cf.[29]). The "rearranged" substitution products *(21)* and *(22)* are formed exclusively by the EA mechanism; consequently, in the competition experiments,



the partial competition constant K_4 is the same as in corresponding competition experiments with 3-chloropyridine and 3-bromopyridine (cf. Fig. 3). The 3-substituted pyridines *(23)* and *(24)*, on the other hand, are formed by both the EA and the AE_n mechanisms. This is shown by the non-linear dependence of the ratio of the 3-substitution products obtained on the ratio of the bases. A non-linearity of this nature is often observed when mechanisms are superimposed (cf. Sections 2.4 and 3.2). It is evidently a typical phenomenon and in the elucidation of substitution mechanisms it therefore provides additional information, which is particularly valuable when *three* mechanisms are superimposed on one another.

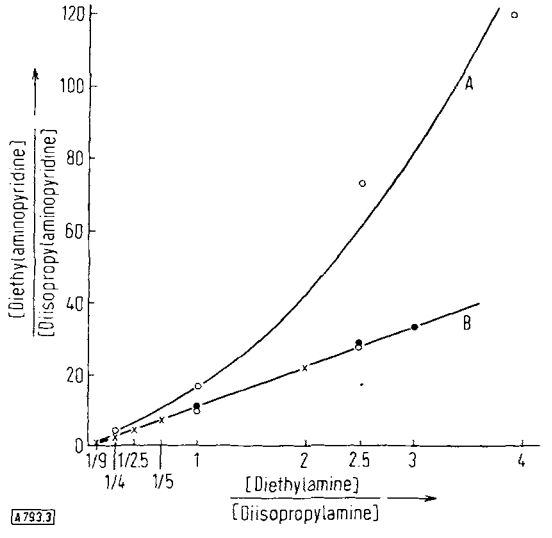


Fig. 3. Competition experiments with 3-fluoropyridine (○) and diethylamine/diisopropylamine by method B [25] (EA/AE_n superposition; evaluation of the 3- and 4-substituted pyridines) and corresponding experiments with 3-chloropyridine (●) and 3-bromopyridine (×) (pure EA mechanism; evaluation only of the 4-substituted pyridines). Curve A: evaluation of the 3-substituted pyridines; line B: evaluation of the 4-substituted pyridines.

As will be shown in Sections 2.3.3 and 2.4, the "base competition method" is also suitable for the detection of AE_n and AE_a mechanisms.

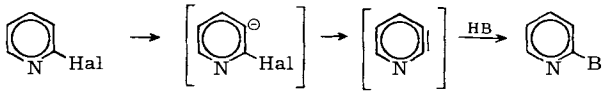
2.3.3. EA/AE_n Competition in Hetaryl Halides with Imidoyl Halide Structures

Halides of six-membered hetarenes having imidoyl halide structures such as 2-halogenopyridines and 2-halogenoquinolines give only 2-substituted hetarenes on reaction with secondary halides or their lithium compounds or even with KNH_2/liquid NH_3 provided that no resinification or tele-substitution (cf. Section 4) occurs.

[33] *G. Wittig* and *M. Rings*, Liebigs Ann. Chem. *719*, 127 (1968).

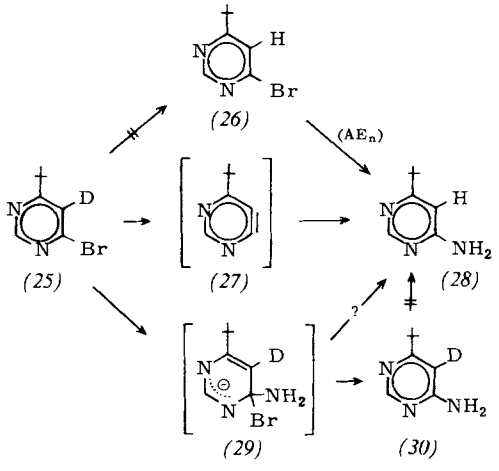
[34] It is assumed here that two positionally isomeric substitution products are formed, as is usual in the EA mechanism.

By analogy with the mechanism of the Chichibabin reaction[35] therefore, these reactions have been assumed to proceed by the AE_n mechanism. However, they could also proceed by an EA mechanism.



According to EHT calculations (cf. Section 2.1), this mechanism is not unlikely, since the 3-pyridyl anion (model of the anionic hetaryne precursor) is relatively poor in energy and 2,3-didehydropyridine is electron-deficient on C-2, which could explain the exclusive uptake of the nucleophile in position 2.

The exclusive formation of the nondeuterated 4-amino compound *(28)* has in fact been observed in the comparable reaction of 4-bromo-6-*tert*-butyl-5-deuteriopyrimidine *(25)* with KNH_2/liquid NH_3 at −75° C; this points very strongly to the EA mechanism *via (27)*[36, 37].



The final elucidation of this problem should be possible by the base-competition method (cf. Section 2.3.2). Unequivocal results were obtained by competition experiments with 2-halogenopyridines (Hal = Cl,Br) using method A[25] and with 2-halogeno-4-methylquinolines (Hal=F,Cl,Br) using method B[39,40], with piperidine/diethylamine as the base pair; as in the corresponding experiments with halogenopyridines and halogenoisoquinolines (see Fig. 2), the product ratio was found to exhibit a strictly linear dependence on the base ratio, and the competition constants were strongly dependent on the halogen (cf. Fig. 4). This rules out a pure EA mechanism in these cases, and suggests a pure AE_n mechanism.

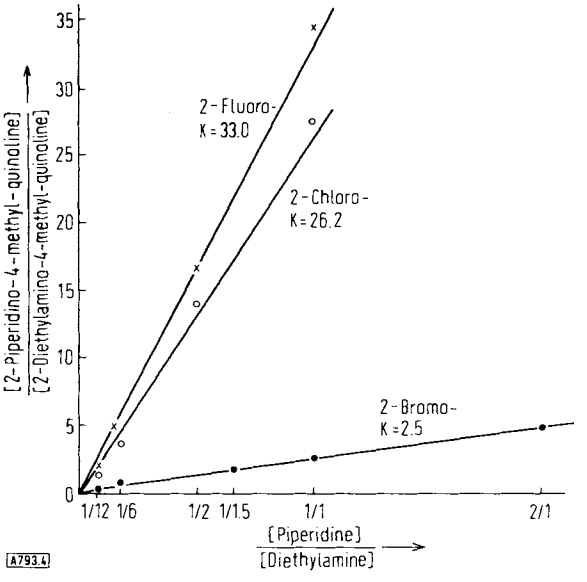


Fig. 4. Competition experiments with 2-halogeno-4-methylquinolines and piperidine/diethylamine (by method B) [39].

With the relatively bulky base pair diethylamine/diisopropylamine (the EA mechanism should be favored by the use of bulky bases, cf. Section 2.3.1), competition experiments on 2-halogenoquinolines (method B, Fig. 5)[41] gave a strictly linear dependence of the product ratio on the base ratio and a high competition constant only for Hal = F, for which the AE_n mechanism is most likely (cf. Section 2.3.1).

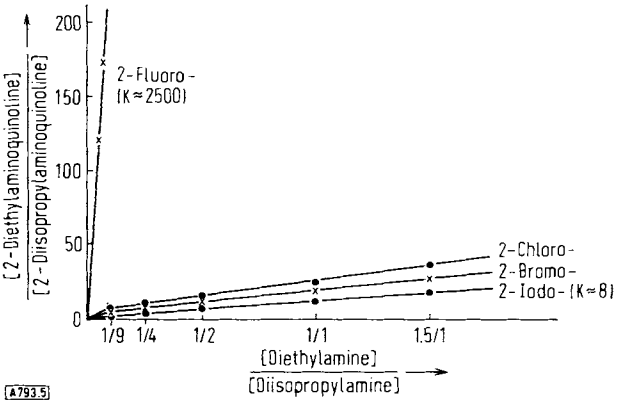


Fig. 5. Competition experiments with 2-halogenoquinolines and diethylamine/diisopropylamine (by method B) [41].

For Hal = Cl, Br, and I, the dependence of the product ratio on the base ratio was not perfectly linear, and the competition constants found were very similar to one another and of the same order of magnitude as in selectivity determinations carried out in the same manner on hetarynes (Tables 3 and 4). This suggests an EA/AE_n superposition with predominance of the EA mechanism for Hal = Cl, Br, and I, but cannot be taken as conclusive proof of the participation of the EA mechanism, the as-

[35] *K. Ziegler* and *H. Zeiser*, Ber. Dtsch. Chem. Ges. *63*, 1847 (1930).

[36] *H. C. van der Plas, P. Smit,* and *A. Koudijs*, Tetrahedron Lett. *1968*, 9.

[37] A D/H exchange *(25)*→*(26)* and *(30)*→*(28)* was ruled out experimentally. A remote possibility [38] would be a D/H exchange on the hypothetical adduct *(29)*. The occurrence of the hetaryne intermediate *(27)* consequently cannot yet be regarded as being absolutely certain.

[38] *Th. Kauffmann, R. Nürnberg,* and *K. Udluft*, Chem. Ber. *102*, 1177 (1969).

[39] *R. Nürnberg*, Dissertation, Universität Münster 1969.

[40] Under the experimental conditions (ether, 35° C), the halogenoquinolines do not react with the free secondary amines [39].

[41] *J. Albrecht*, Dissertation, Universität Münster, 1970.

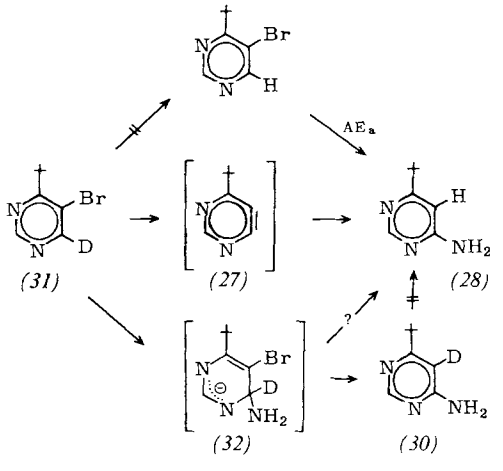
sumption of which also implies the exclusive uptake of the nucleophile in position 2 of the hypothetical 2,3-didehydroquinoline.

2.4. EA/AE$_a$ Competition in Nucleophilic Substitutions

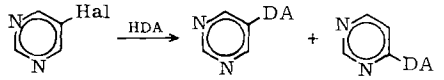
The observation of cine-substitutions on reaction of hetaryl halides with bases has led in several cases to the discovery of a hetaryne. Reactions of this type are not, however, a reliable indication of the occurrence of a hetaryne intermediate, since 2-bromobenzo[*b*]thiophene *S*,*S*-dioxide reacts with piperidine in ethanolic solution by an anomalous addition-elimination mechanism (AE$_a$) to give the 3-piperidino compound[42].

On theoretical grounds (see below), it seemed probable[3] that the AE$_a$ mechanism also plays a part in the cine-substitution reactions observed by three groups of workers in 1964 with 5-halogenopyrimidines (cf.[38]). Two of these reactions have been investigated more closely.

Van der Plas et al.[36] studied the reaction of 5-bromo-6-*tert*-butyl-4-deuteriopyrimidine *(31)* with KNH_2/liquid NH_3. The resulting cine-substitution product *(28)* contained no deuterium, and the starting compound *(31)* and the deuterated amino compound *(30)* did not undergo D/H exchange under the experimental conditions. If it is assumed that no D/H exchange takes place in *(32)*, this means that the cine-substitution proceeds *via* the hetaryne *(27)* and not *via* the anomalous adduct *(32)* (intermediate of the AE$_a$ mechanism)[43].

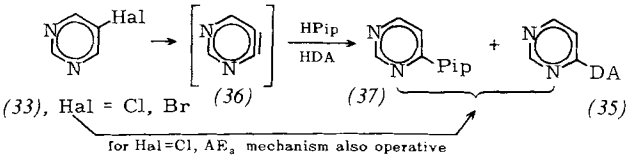


Kauffmann et al.[38, 44] allowed 5-halogenopyrimidines *(33)* (Cl, Br) to react with diethylamine at 130 °C (autoclave) to form *(34)* and *(35)*. The ratio of *(34)* to *(35)* was found to vary with the halogen (82/18 for Hal = Cl; 40/60 for Hal = Br), ruling out a pure EA mechanism. The strong predominance of the "unrearranged" compound *(34)* points to the probable participation of the AE$_n$ mechanism in the reaction of 5-chloropyrimidine[45]. The participation of the EA mechanism was deduced from interception experiments with aniline and the inhibition of the cine-substitution *(33b)* → *(35)* by ethanol[38], which will be discussed below.



(33a), Hal = Cl *(34)* *(35)*
(33b), Hal = Br

To study the cine-substitutions further, the halides *(33a)* and *(33b)* were allowed to react with piperidine/diethylamine in competition experiments (method A; Section 2.3.2). The cine-substitution products *(37)* and *(35)* were formed in addition to other compounds[38].



If these were formed exclusively by the EA mechanism, the experimental points in Figure 6 should lie on a single straight line (cf. Section 2.3.2).

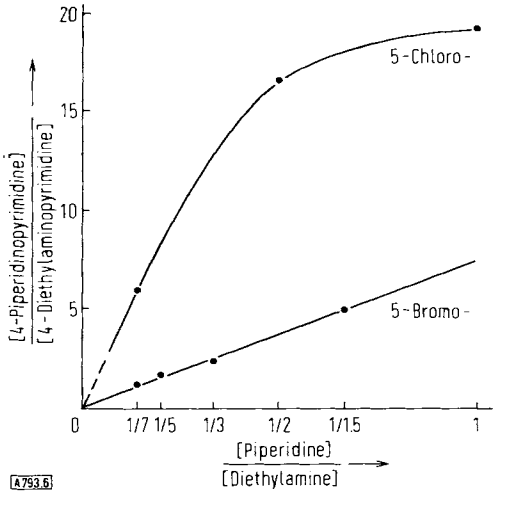


Fig. 6. Competition experiments with 5-halogenopyrimidines and piperidine/diethylamine (130 °C); evaluation of the cine-substitution products [38].

Since this is not so, a second cine-substitution mechanism must also be involved; this second mechanism must operate in the case of 5-chloropyrimidine, since the dependence of the *(37)*/*(35)* ratio on the molar ratio of the competing secondary amines was distinctly nonlinear in this case (typical of the superposition of two mechanisms; cf. Section 2.3.2). The second mechanism is probably the AE$_a$ mechanism, for which the conditions are particularly favorable in the 5-halogenopyrimidines, since the addition of a base in position 4 leads to an anomalous adduct *(38)*, in which, unlike in the normal adduct (base residue on C-5), the negative charge in-

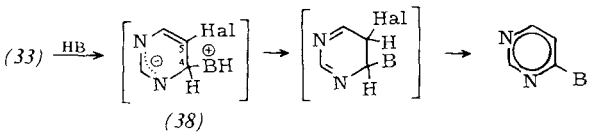
[42] *F. G. Bordwell, B. B. Lampert,* and *W. H. McKellin,* J. Amer. Chem. Soc. *71,* 1702 (1949).

[43] According to *H. C. van der Plas,* Tetrahedron Lett. *1965,* 555, a small quantity of 5-amino compound is formed as well as the 4-amino compound (4-isomer/5-isomer ratio 93:7) in the reaction of 5-bromo-6-*tert*-butylpyrimidine with KNH_2/liquid NH_3.

[44] *Th. Kauffmann, R. Nürnberg,* and *K. Udluft,* Angew. Chem. *80,* 614 (1968); Angew. Chem. internat. Edit. *7,* 617 (1968).

[45] AE$_n$ mechanism more favored in chlorides as compared with bromides (cf. Section 2.3.1).

troduced is taken over by two N atoms; this explains the intermediate occurrence of *(38)* (Hal = Cl) in addition to the energy-rich hetaryne *(36)*.



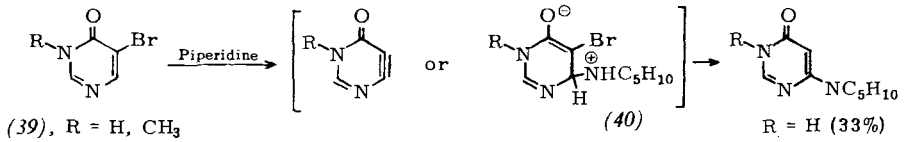
(38)

An additional and important argument in favor of the EA mechanism in the case of the bromo compound *(33b)* and the participation of the AE_a mechanism in the case of the chloro compound *(33a)* is the observation[38] that the cine-substitution in *(33b)* is completely suppressed by the *addition of ethanol* (protonation of the anionic hetaryne precursor), whereas practically no inhibition occurs in the reaction of *(33a)*[46].

Thus 5-chloropyrimidine very probably reacts with the secondary amines used by EA + AE_n + AE_a, whereas the bromo compound reacts by EA or EA + AE_n.

Good possibilities for the AE_a mechanism are theoretically also offered by hetaryl halides with a carbonyl group in the ring α to the halogen, since corresponding anomalous adducts, *e.g. (40)*, should be relatively poor in energy.

However, in the more intensively studied nucleophilic cine-substitutions of 3-halogeno-2-quinolones (reaction with piperidine at 180° C), in which a group of this type is present, only evidence of the EA mechanism was found (including constancy of the isomer ratio when the halogen is varied)[47]. Further investigations on the mechanisms of similar reactions of 3-chloro-1-methyl-2-pyridone[38], 5-bromouracil[3,48], 4-halogeno-1-methyl-2-phenylpyridazine-3,6-diones[49], and *(39)*[50] are necessary.



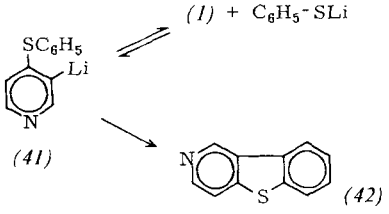
(39), R = H, CH_3 *(40)*

R = H (33%)

R = CH_3 (62%)

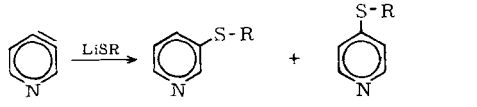
2.5. New Hetaryne Interception Reactions

9,10-Didehydrophenanthrene formed in ether by the action of lithium piperidide on 9-bromophenanthrene can be smoothly intercepted with lithium thiophenolate, since this reagent adds to the aryne much more rapidly than lithium piperidide[51]. In attempts to intercept 3,4-didehydropyridine *(1)* (formed in the same manner from 3-chloropyridine) with lithium thiophenolate, the expected thio ethers *(43a)* and *(44a)* could not be detected in the reaction mixture[52]. The reason for this may be that the addition products of lithium thiophenolate with *(1)* [*e.g. (41)*] either readily decompose further [*(1)* would then be removed from the equilibrium by irreversible addition of lithium piperidide] or cyclize with loss of lithium hydride to form thiophene derivatives [*e.g. (42)*]. Analogies are known for both possibilities[53].



(41) *(42)*

It was recently found[54] that the reaction of 3-bromopyridine or 4-chloropyridine with $NaNH_2$/liquid NH_3 in the presence of sodium methanethiolate (sixfold ex-



(1) *(43a)*, R = C_6H_5 *(44a)*, R = C_6H_5

(43b), R = CH_3 *(44b)*, R = CH_3

cess) yields *(43b)* and *(44b)* (molar ratio 1:1) in addition to 3- and 4-aminopyridines. Since the weakly basic sodium methanethiolate is unable to react with these two halogenopyridines, the products must result from interception of the hetaryne intermediate. Sodium methanethiolate may be regarded in general as a promising reagent for the interception of hetarynes.

On addition of furan to a solution of the lithium compounds *(45)* (R = NC_5H_{10}, OCH_3) in ether, the adducts *(47)* are formed in yields of 45%[55] and 35%[56] respectively. These reactions point to the intermediate formation of the 2,3-didehydropyridine derivatives *(46)*.

[46] The fact that the addition of ethanol causes practically no inhibition of the cine-substitution in the case of 5-chloropyrimidine, though the EA component should be suppressed by ethanol when EA and AE_a mechanisms occur together, can be explained by promotion of the AE_a mechanism by ethanol.

[47] *Th. Kauffmann* and *J. Schulz*, Chem. Ber. *99*, 1837 (1966).

[48] *K. Forberger*, Diplomarbeit, Technische Hochschule Darmstadt 1965; *M. Schönfelder*, Diplomarbeit, Universität Münster 1966.

[49] *Th. Kauffmann, A. Risberg, J. Schulz*, and *R. Weber*, Tetrahedron Lett. *1964*, 3563; *A. Risberg*, Dissertation, Technische Hochschule Darmstadt 1969.

[50] *R. Promel, A. Cardon, M. Daniel, G. Jacques*, and *A. Vandersmissen*, Tetrahedron Lett. *1968*, 3067. "Unrearranged" substitution products were apparently not found.

[51] *R. Huisgen* and *J. Sauer*, Angew. Chem. *72*, 105 (1960).

[52] *F.-P. Boettcher*, Dissertation, Techn. Hochschule Darmstadt, 1961.

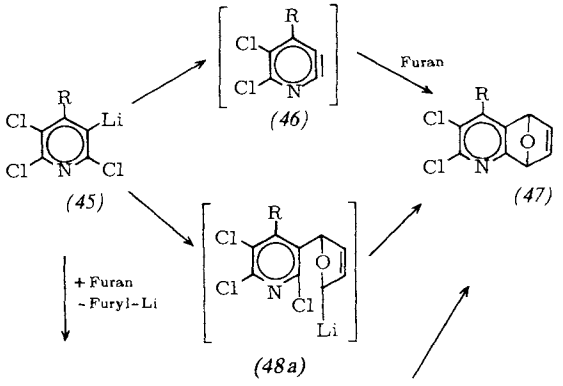
[53] Cf. the reversible addition of sodium thiophenolate to didehydrobenzene and the formation of dibenzothiophene with elimination of lithium hydride from *o*-lithium diphenyl sulfide: *F. Scardizlia* and *J. D. Roberts*, Tetrahedron *3*, 197 (1958); *J. F. Bunnett* and *T. K. Brotherton*, J. Org. Chem. *23*, 904 (1958); *A. Lüttringhaus, G. Wagner-v. Sääf, E. Sucker*, and *G. Borth*, Liebigs Ann. Chem. *557*, 46 (1947).

[54] *J. A. Zoltewicz* and *C. Nisi*, J. Org. Chem. *34*, 765 (1969).

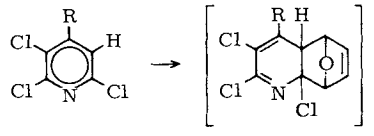
[55] *J. D. Cook* and *B. J. Wakefield*, Chem. Commun. *1968*, 297. Similar reactions of 2,3,5,6-tetrachloro-4-lithiopyridine with benzene, mesitylene, and durene, which probably proceed *via* 2,5,6-trichloro-3,4-didehydropyridine: cf. *J. D. Cook* and *B. J. Wakefield*, Chem. Commun. *1967*, 2535.

[56] *R. A. Fernandez, H. Heaney, J. M. Jablonski, K. G. Mason*, and *T. J. Ward*, J. Chem. Soc. *C 1969*, 1908.

However, caution is necessary in view of the findings (cf. Section 3.1) with five-membered hetaryl halides. These reactions can therefore be accepted as showing the occurrence of *(46)* only if the conceivable routes *via (48a)* and *(48b)* can be experimentally ruled out.

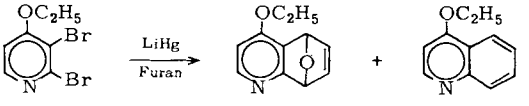


(45) *(46)* *(47)* *(48a)*



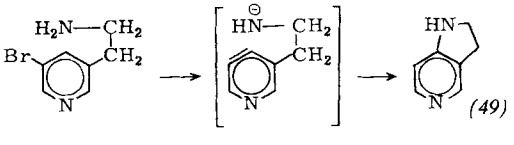
(48b)

Similar uncertainty exists in connection with the course of the reaction of 4-ethoxy-2,3-dibromopyridine with lithium amalgam and furan[57], as well as similar reactions that have been known for some time[58,59].

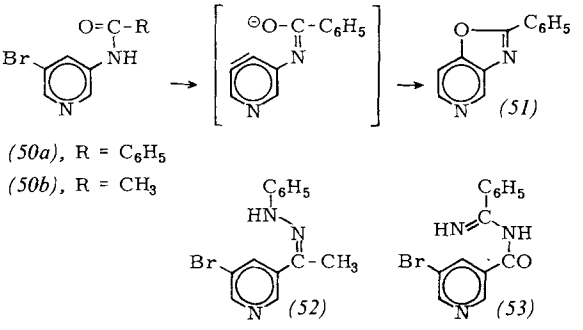


2.6. Side-Chain Cyclization

Some 100 examples (cf.[4]) of the cyclization of a side chain by intramolecular addition of a nucleophilic center to the aryne bond are known in the carbocyclic series. The application of this principle to hetarynes could be very useful for the synthesis of new heterocycles. It appears, however, that only two reactions of this type are known at present: Reaction of three equivalents of phenyllithium and 1.2 equivalents of diethylamine in boiling ether with 3-(β-aminoethyl)-5-bromopyridine leads to 2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine *(49)*[60] in 56% yield. Similarly, the action of an excess of lithium piperidide on 3-benzamido-5-bromopyridine *(50a)* in boiling ether gave 2-phenyloxazolo[4,5-*c*]pyridine *(51)* in 8% yield[60]; the low yield is partly due to the fact that *(51)* is unstable under the reaction conditions. No cyclization products could be isolated in similar reactions with *(50b)*, *(52)*, and *(53)*[60].



(49)



(50a), R = C_6H_5
(50b), R = CH_3

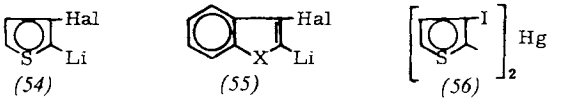
(51) *(52)* *(53)*

3. Five-Membered Hetarynes

3.1. Containing One Hetero Atom

After careful analysis of the existing results on five-membered hetarynes, *R. W. Hoffmann*[4] concluded in 1967 that: "in fact no unambiguous evidence is as yet available for the formation of dehydro-derivatives of five-membered aromatic heterocycles". This situation has not changed in the meantime for five-membered hetarynes containing *one* hetero atom.

The reasons for the evident lag in relation to the chemistry of six-membered hetarynes are as follows:
1) *o*-Metalated five-membered hetaryl halides of the types *(54)*-*(56)* and related compounds that were promising hetaryne precursors have proved to be surprisingly stable. In their thermal decomposition, moreover, they always follow reaction paths that avoid a five-membered hetaryne intermediate[4,33].



(54) *(55)* *(56)*

2) The only method used so far for the attempts to detect five-membered hetarynes containing one hetero atom is interception with dienes. However, the corresponding hetaryl halides whose *o*-alkali metal or *o*-mercury compounds were used can often react with dienes, as in the example below. Since these hetaryl halides are formed from the *o*-alkali metal and *o*-mercury compounds by protolysis or thermal decomposition in the reaction mixture, this sometimes gave the impression of the occurrence of five-membered hetarynes, while in other cases it casts doubt on previous assumptions of five-membered hetaryne intermediates[4,33].

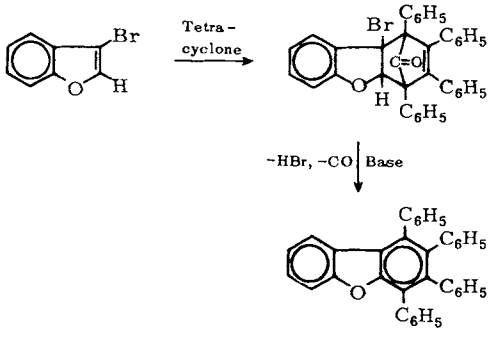
To clarify the mechanism, the cine-substitutions indicated below should now be investigated by methods that have been successful in the detection of six-membered hetarynes [checking for

[57] *H. N. M. van der Lans* and *H. J. den Hertog*, Recl. Trav. Chim. Pays-Bas *87*, 549 (1968).

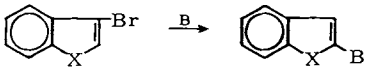
[58] *R. J. Martens* and *H. J. den Hertog*, Tetrahedron Lett. *1962*, 643.

[59] *Th. Kauffmann* and *K. Udluft*, Angew. Chem. *75*, 89 (1963); Angew. Chem. internat. Edit. *2*, 45 (1963).

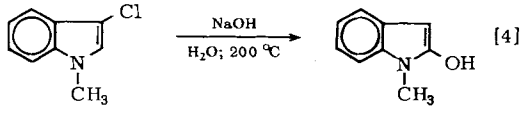
[60] *Th. Kauffmann* and *H. Fischer* (Dissertation, Universität Münster, probably 1971), unpublished experiments 1969/1970.



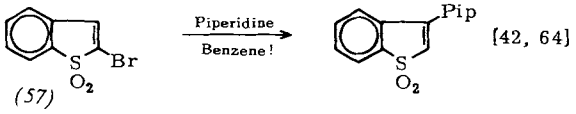
constancy of the isomer ratio on variation of the halogen in the starting compound (where unrearranged products are also formed)[31]; "base competition method" (cf. Section 2.3.2); use of deuterated starting halides (cf. Sections 2.3.3 and 2.4)].



X = O; B = $C_2H_5O^{\ominus}$, 200 °C in C_2H_5OH [61]
X = S; B = $HO^{\ominus}$, 200 °C in C_2H_5OH [62]
X = S; B = Piperidine, 250 °C [63]



[4]

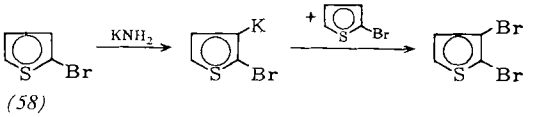


[42, 64]

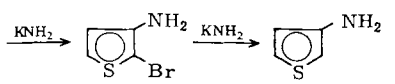
(57)

Owing to the high stability of lithium compounds of the types *(54)* and *(55)*, which is partly due to the inductive effect of the hetero atom in the ring, and because of the expected strong ring strain in five-membered hetarynes, the prospects for the AE_a mechanism in the cine-substitutions formulated above would be good[4]. On the other hand, unlike the N atom of the pyridine system or the $-SO_2-$ group in 2-bromobenzo[*b*]thiophene *S,S*-dioxide *(57)* (AE_a mechanism in ethanol[42]), the hetero atoms O,S, and N in five-membered hetarenes lead to an excess of π electrons on the C atoms of the heterocyclic ring, which must make nucleophilic additions introducing an AE_a (or AE_n) mechanism more difficult.

It is interesting in this connection to note that convincing evidence has been accumulated in favor of a "Reinecke mechanism" for the nucleophilic cine-substitution *(58)*→*(59)*[65] which significantly avoids both a five-membered hetaryne intermediate and an anomalous addition to the excess π-electron system.



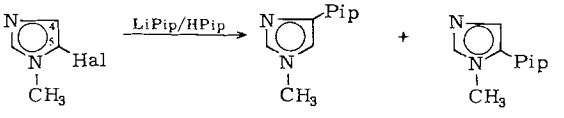
(58)



(59) (59%)

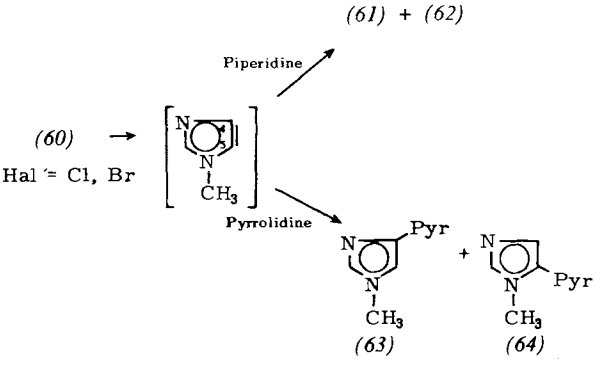
3.2. Containing Two Hetero Atoms

Cine-substitutions on five-membered hetarenes containing two hetero atoms have only recently been discovered[32]. 5-Halogeno-1-methyl-imidazoles *(60)* (Hal = Cl, Br) react with lithium piperidide/piperidine in ether at 35 °C to give 4- *(61)* and 5-piperidino-1-methylimidazole *(62)*. The very clear dependence of the *(61)*/*(62)* ratio on the halogen in the starting compound (9/91 for Hal = Cl and 36/64 for Hal = Br[66]) rules out a pure EA mechanism. The strong preference for the formation of the "unrearranged" isomer points to the participation of an AE_n mechanism in the case of the chloro compound.



(60a), Hal = Cl *(61)* *(62)*
(60b), Hal = Br

In competition experiments with pyrrolidine/piperidine (method B, cf. Section 2.3.2), the substitution products *(61)*–*(64)* were formed.



(61) + *(62)*

Hal = Cl, Br

(63) *(64)*

The fact that the partial competition constant $K_4 = 2.2$ (line A in Fig. 7) is independent of the nature of the halogen (Cl, Br) leaves little doubt that the rearranged substitution products *(61)* and *(63)* are formed exclusively by the EA mechanism *via* 4,5-didehydro-1-methylimidazole.

For the formation of the substitution products *(62)* and *(64)* from the 5-chloro compound *(60a)* (curve B in Fig. 7), the non-linear dependence of the *(62)*/*(64)* ratio on the ratio of the competing secondary amines points to the superposition of the EA and a second substitution mechanism (presumably AE_n). The formation of the unrearranged substitution product from the bromo compound *(60b)* (line C in Fig. 7), on the other hand, also appears to proceed exclusively by the EA mechanism, in view of the linear dependence of the product ratio on the base ratio.

[61] *R. Stoermer* and *B. Kahlert*, Ber. Dtsch. Chem. Ges. *35*, 1633 (1902). The cine-substitution product was detected in the form of secondary products.

[62] *G. Komppa* and *S. Weckman*, J. Prakt. Chem. [2] *138*, 109 (1933).

[63] *K. R. Brower* and *E. D. Amstutz*, J. Org. Chem. *19*, 411 (1954).

[64] In benzene this cine-substitution does not proceed exclusively *via* the anomalous adduct mentioned in Section 2.4 [42].

[65] *M. G. Reinecke* and *H. W. Adickes*, J. Amer. Chem. Soc. *90*, 511 (1968).

[66] Molar ratio halide : lithium piperidide : piperidine = 1 : 2.2 : 2.8.

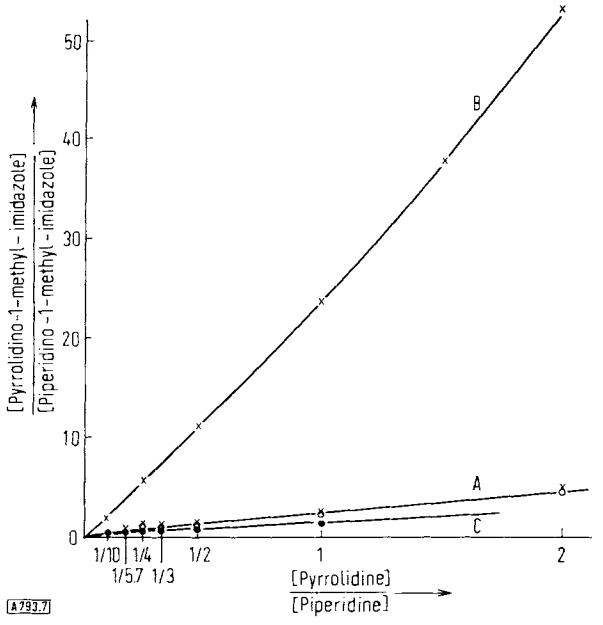


Fig. 7. Competition experiments with 5-halogeno-1-methylimidazoles *(60)* and pyrrolidine/piperidine (by method B) [32]. Line A: 4-substitution products *(61)* and *(63)* formed from *(60a)* (×) or *(60b)* (○); Line B: 5-substitution products *(62)* and *(64)* formed from *(60a)*; Line C: 5-substitution products *(62)* and *(64)* formed from *(60b)*

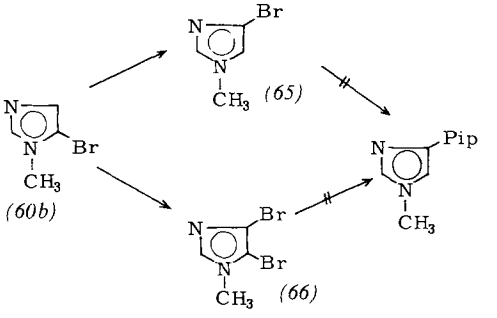
This is also indicated by the fact that the ratios (Table 8) of the quantities of isomeric pyrrolidino compounds *(63)/(64)* and of the piperidino compounds *(61)/(62)* are largely independent of the pyrrolidine/piperidine ratio. The isomer ratios found (approx. 68:32 and 72.5:27.5, respectively) apparently correspond to the aryne ratio for 1-methyl-4,5-didehydroimidazole and the bases pyrrolidine and piperidine.

Since 5-bromo-1-methylimidazole *(60b)* gives the 4-bromo compound *(65)* (yield 30%) on reaction with KNH_2/liq. NH_3[67], it seemed not unreasonable to assume

Table 8. Competition experiments with the 5-halogeno-1-methylimidazoles *(60)*; isomer ratios of the resulting pyrrolidino compounds *(63)* and *(64)* and piperidino compounds *(61)* and *(62)*.

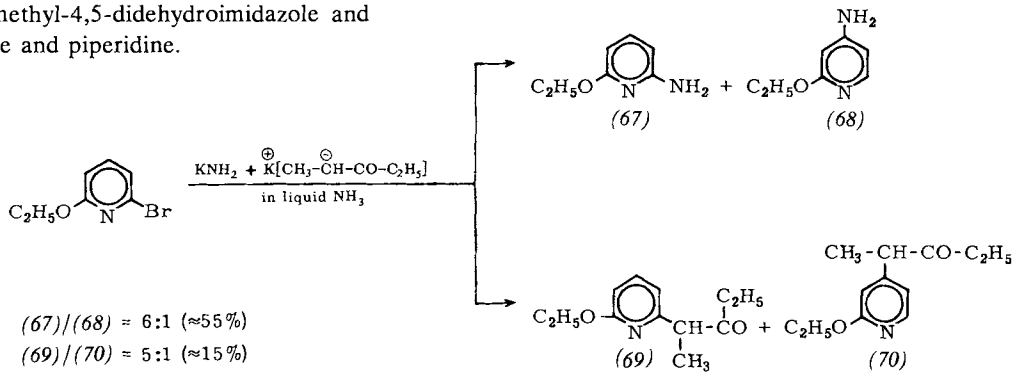
Halogen	[Pyrrolidine] / [Piperidine]	*(63)* : *(64)*	*(61)* : *(62)*
Cl	1:1	30:70	72:28
	1:2	18:82	60:40
	1:3	17:83	59:41
	1:4	16:84	54:46
Br	1:1	70:30	74:26
	1:2	67:33	72:28
	1:3	67:33	73:27
	1:4	67:33	71:29

that the above cine-substitutions, as formulated below for the piperidino compound, proceed *via* 4-halogeno-1-methylimidazoles. However, 4-chloro-1-methylimidazole and 4-bromo-1-methylimidazole do not react with lithium piperidide/piperidine in boiling ether to form 4-piperidino-1-methylimidazole[41]. Since the same is true of 4,5-dibromo-1-methylimidazole *(66)*, a cine-substitution mechanism involving an *o*-dihalogeno intermediate, as postulated by *Reinecke* for the thiophene system[65], may be ruled out, at least for 4-bromo-1-methylimidazole.



4. The Problem of *m*-Didehydrohetarenes

Though *m*-didehydrohetarenes are not hetarynes (= *o*-didehydrohetarenes) it seems appropriate to mention these compounds, which are purely hypothetical at present. According to EHT calculations[5] (Table 1), the hypothetical 2,4-didehydropyridine *(2)* is richer in



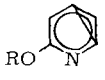
energy than 3,4-didehydropyridine, but poorer in energy than 2,3-didehydropyridine, for whose occurrence as an intermediate there are many indications[2-4]. It is therefore interesting to observe that in reactions of 2-bromopyridines containing a substituent ($-OCH_3$, $-OC_2H_5$, $-OC_3H_7$, $-C_6H_5$) in position 6 with KNH_2/liquid NH_3, *den Hertog et al.*[8,68,69] isolated tele-substitution products in which the new substituent occupies position 4, as in *(68)* and *(70)*. as well as "unrearranged" substitution products.

[67] *D. A. de Bie* and *H. C. van der Plas*, Recl. Trav. Chim. Pays-Bas *88*, 1246 (1969); references given there for similar halogen migrations in halogenobenzenes, halogenopyridines, halogenothiophenes, and halogeno-3-methylisothiazoles.

[68] *M. J. Pieterse* and *H. J. den Hertog*, Recl. Trav. Chim. Pays-Bas *80*, 1376 (1961).

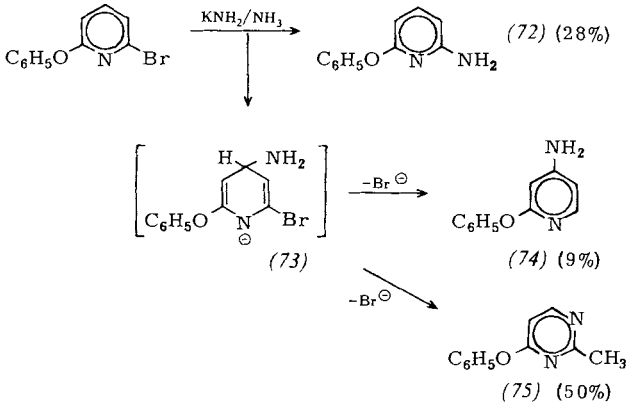
[69] *J. W. Streef* and *H. J. den Hertog*, Tetrahedron Lett. *1968*, 5945.

An EA mechanism *via* 2,4-didehydropyridine intermediates *(71)* has been proposed for these reactions[8], since *(70)* was obtained as well as *(67)–(69)* on reaction of 2-bromo-6-ethoxypyridine with KNH_2 and potassium oxopentanide, whereas only the "unrearranged" substitution product *(69)* was formed with potassium oxopentanide alone.



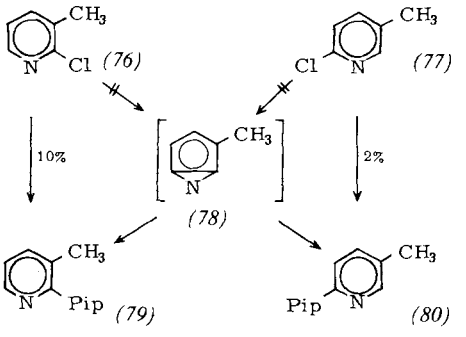
(71)

These tele-substitutions can be readily explained by an AE_a mechanism *via* an anomalous adduct of the type *(73)*[70], since it is well known that potassium amide adds readily to C-4 of the pyridine system if C-2 and C-6 are substituted otherwise than with hydrogen. That one of



the substituents in these positions may be halogen is shown by the ring transformations observed for 2-halogenopyridines and 2-halogenoquinolines[27,69,71] which are introduced by the addition of the amide ion to position 4. In the reaction of 2-bromo-6-phenoxypyridine with KNH_2/liquid NH_3, for example, the ring transformation to form the pyrimidine derivative *(75)* competes with the substitution to give *(72)* ("normal") and *(74)* ("tele"). It seems plausible to assume the common intermediate *(73)* for the tele-substitution and the ring transformation.

The intermediate occurrence of 2,6-didehydropyridine and its methyl derivatives [*e.g. (78)*] was proposed[3] as a reason for the surprising observation that 2-chloropyridine and its 3- and 5-methyl derivatives resinify on reaction with lithium piperidide/piperidine (ether, 35 ° C), and give only a very small yield of the corresponding 2-piperidinopyridine[3], whereas the 2-piperidino compound is formed in 75% yield from the 6-methyl derivative[3] and in 95% yield from 2-chloroquinoline[26]. Since it has been found[72] since then that the tele-substitutions *(76)→(80)* and *(77)→(79)* fail to occur under the same conditions, and since 2,6-didehydropyridine, according to EHT calculations, is the richest in energy of all the didehydropyridines[5], it now seems very unlikely that the above resinification reactions involve 2,6-didehydropyridine intermediates.



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German version: Angew. Chem. *83*, 21 (1971)
Translated by Express Translation Service, London

[70] *Th. Kauffmann*, Discussion remark at the Organic Chemistry Colloquium at Universität Münster, 1969. It would then have to be assumed that KNH_2 catalyzes the AE_a mechanism leading to *(70)*.

[71] *H. J. den Hertog, H. C. van der Plas, M. J. Pieterse*, and *J. W. Streef*, Recl. Trav. Chim. Pays-Bas *84*, 1569 (1965); *J. W. Streef* and *H. J. den Hertog, ibid, 88*, 1391 (1969).

[72] *Th. Kauffmann* and *M. Vestweber*, unpublished experiments, 1965.

1,4-Benzodiazepines. Chemistry and Some Aspects of the Structure-Activity Relationship

By Leo H. Sternbach[*]

Numerous clinically used compounds having favorable tranquilizing and toxic properties possess the 1,4-benzodiazepine skeleton. This group of active substances is readily accessible, e.g. by ring enlargement of quinazoline derivatives, by ring contraction of benzoxadiazocines, and by synthesis from aminobenzophenones, constructing the seven-membered ring in many cases in one step. The relationships between type and position of substituents and the pharmacological properties are illustrated using 1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-ones as examples.

1. General Introduction

This review is meant to give a short outline of the history of the discovery and further development of the chemistry of tranquilizers of the 1,4-benzodiazepine type. It will be limited with very few exceptions to published and also unpublished work carried out in our laboratories[**]. It will concern itself mainly with the most important synthetic routes leading to pharmacologically and clinically interesting types of 1,4-benzodiazepines, and will contain also a short discussion of the pharmacological properties of these compounds.

In view of this, the main subject will be 5-phenyl-1,4-benzodiazepine derivatives which are the most extensively studied group. It should, however, be pointed out that most of the reactions have been used for the synthesis and transformations of 1,4-benzodiazepine derivatives bearing substituents other than phenyl on C-5.

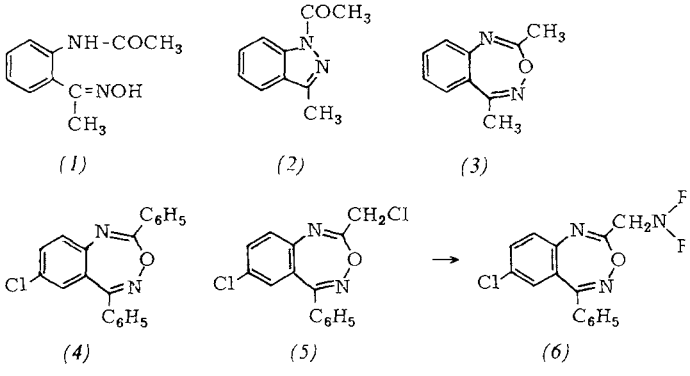
2. Introduction

In the search for a new class of drugs possessing tranquilizing properties similar to those of meprobamate and chlorpromazine, it was decided in the middle 1950's to investigate new types of heterocycles which might ultimately lead to compounds showing the desired properties. As a rather neglected group of chemically interesting compounds, we selected the benzheptoxdiazines, as they were called in the German scientific literature.

The first compounds of this type were obtained in 1891 by *von Auwers* and *von Meyenburg*[1] by dehydration of *o*-acylamino ketoximes *(1)* or aldoximes with a Beckmann mixture. At that time they were considered to be acylindazoles *(2)*.

These compounds were further studied in 1893[2] and reinvestigated in 1924[3] when it was agreed upon that they are best represented by structure *(3)*.

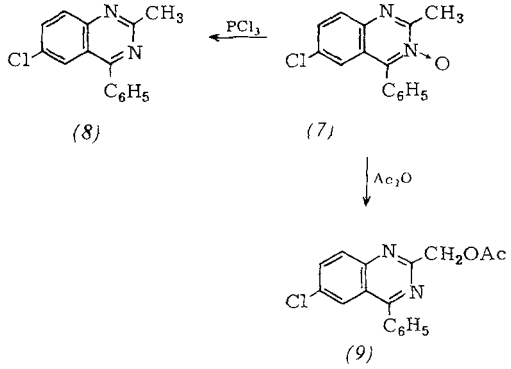
In the mid thirties, a few further members of this class of compounds were prepared, specifically compound *(4)*[4] and close analogs thereof. They were relatively easy to synthesize, crystallized very well, and were easy to purify. These were the reasons which made this group of heterocycles so attractive for further exploration. Derivatives to which basic substituents could be attached, as illustrated by conversion of *(5)* into *(6)*, appeared to be particularly interesting.



(1) *(2)* *(3)*

(4) *(5)* *(6)*

Closer chemical study of these compounds led to the conclusion that the so called "benzheptoxdiazines" did not have the structure originally assigned to them, but were in fact quinazoline 3-oxides of type *(7)*. The transformations shown below illustrate the structural proof[5]. The *N*-oxide oxygen could be readily removed by treatment with phosphorus trichloride or by catalytic hydrogenation to yield the quinazoline *(8)*. On the other hand, treatment with acetic anhydride resulted in the



(8) *(7)* *(9)*

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[**] For a complete review see *G. A. Archer* and *L. H. Sternbach*, Chem. Rev. *68*, 747 (1968).

[1] *K. von Auwers* and *F. von Meyenburg*, Chem. Ber. *24*, 2370 (1891).

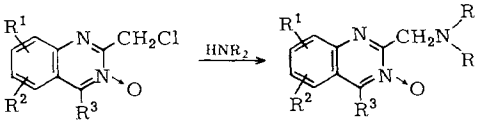
[2] *A. Bischler*, Chem. Ber. *26*, 1891, 1901 (1893).

[3] a) *J. Meisenheimer* and *A. Diedrich*, Chem. Ber. *57*, 1715 (1924); b) *K. von Auwers*, *ibid.* *57*, 1723 (1924).

[4] *K. Dzieworński* and *L. H. Sternbach*, Bull. Intern. Acad. Polonaise, Classe Sc. Math. Nat. Ser. A, 333–348 (1935); Chem. Abstr. *30*, 2972 (1936).

[5] *L. H. Sternbach*, *S. Kaiser*, and *E. Reeder*, J. Amer. Chem. Soc. *82*, 475 (1960).

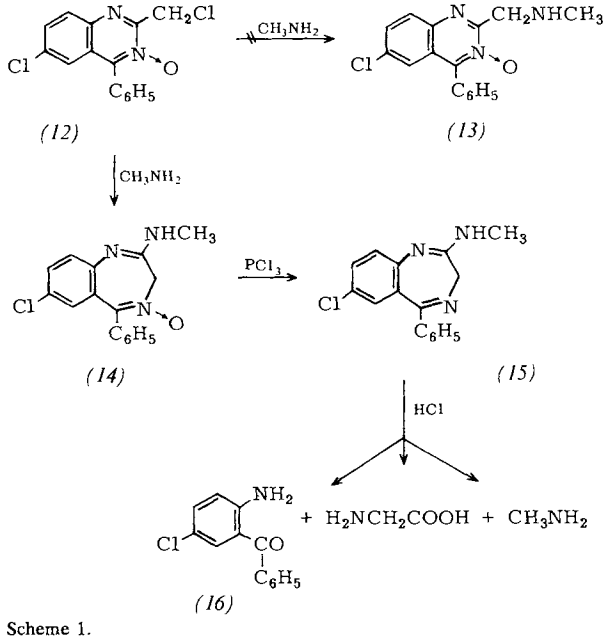
formation of the acetoxy derivative *(9)*, a transformation analogous to that of picoline *N*-oxide[6]. The interesting novel structure of these compounds lending itself to a variety of transformations led to intensified studies. These resulted first in the synthesis of a number of quinazoline 3-oxides of the general formula *(10)* and their transformations with various amines. Secondary amines generally yielded normal substitution products of type *(11)*, which showed no particularly interesting biological properties. The reaction with primary amines or ammonia, however, resulted in the formation of pharmacologically very attractive compounds.



(10) *(11)*

3. Ring Enlargement of Quinazoline 3-Oxides by Treatment with Amines

The products obtained on treatment of compounds of type *(10)* with primary amines were the result of an unusual, novel ring enlargement. Scheme 1 shows the first compound *(14)* thus obtained, and gives a short outline of the structural proof[7].



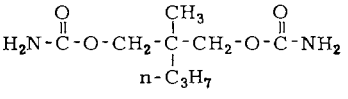
Scheme 1.

Compound *(14)* had the expected composition, was monomolecular, contained an *N*-oxide function and a secondary methylamino group. The UV and IR spectra indicated, however, that the quinazoline 3-oxide molecule must have undergone very profound changes and that the reaction product could not be *(13)*, the simple substitution product. This was confirmed by chemical studies which showed ultimately that the compound had the structure of a 1,4-benzodiazepine 4-oxide *(14)*, and was a representative of a novel group of heterocycles.

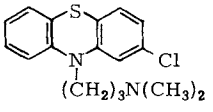
The structure was established by classical methods before the widespread use of NMR and mass spectroscopy became commonplace. It consisted in the acid hydrolysis of the deoxy derivative *(15)* which gave an excellent yield of the aminobenzophenone *(16)*. In addition, glycine and methylamine were formed, which, after benzoylation, were isolated from the hydrolysis mixture in over 60% yield. The normal substitution product *(13)*, on oxygen removal and hydrolysis, would have yielded *N*-methylglycine and ammonia in addition to the aminobenzophenone (see Scheme 1).

4. Pharmacology of Chlordiazepoxide

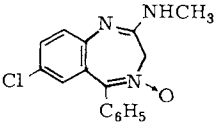
This compound *(14)*, which later obtained the generic name chlordiazepoxide was, as mentioned above, the first product to show desirable pharmacological properties. It was a sedative, muscle relaxant, and anticonvulsant resembling in many respects meprobamate and chlorpromazine, the then most used tranquilizers. Extended pharmacological and later, clinical studies confirmed these properties and led to its introduction in 1960 as the active ingredient of the specialty Librium®. Table 1 shows the comparison of its pharmacological properties and toxicity with those of the two aforementioned tranquilizers.



Meprobamate



Chlorpromazine



(14)

The top row shows the primary tests which were and are generally used in our Pharmacology Department to demonstrate sedative and "tranquilizing" properties. The first test (Inclined Screen) indicates sedation and muscle relaxation in mice, the second (the fighting mice test) a taming effect, and the third measures muscle relaxation in cats. The antimetrazole (Cardiazol) shock test is a measure of sedation and anticonvulsant activity, whereas the two electroshock tests indicate pure anticonvulsant properties[8]; the last column shows the toxicity. The figures in the table indicate the amounts of material (mg/kg) needed to achieve the desired effect. Therefore, small numbers indicate high potency and high numbers low activity[*].

[6] *V. Boekelheide* and *W. J. Linn*, J. Amer. Chem. Soc. *76*, 1286 (1954); *O. H. Bullitt Jr.* and *J. T. Maynard*, *ibid.* *76*, 1370 (1954).

[7] *L. H. Sternbach* and *E. Reeder*, J. Org. Chem. *26*, 1111 (1961).

[8] *L. H. Sternbach*, *L. O. Randall*, *R. Banziger*, and *H. Lehr* in *A. Burger:* Drugs Affecting The Central Nervous System. Marcel Dekker, New York 1968, Vol. 2, Chap. 6.

[*] All the pharmacological data reported subsequently will be presented in the same manner in tables containing the same tests in the same order. The toxicity data will be omitted since all benzodiazepine derivatives of the type discussed show a very low toxicity. In view of the wide variations found in biological tests, differences of ± 50% are meaningless. For detailed descriptions of the tests see [8].

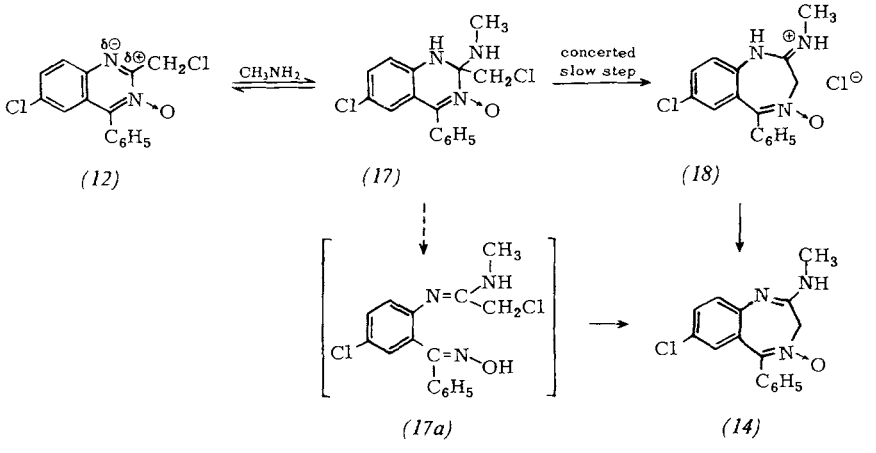
Table 1. Pharmacological and toxic properties of meprobamate, chlorpromazine, and chlordiazepoxide. For explanation see text.

Compound	Incl. Screen	Fighting Mice	Cat	Anti-Met.	Electroshock Max.	Min.	LD_{50} p.o.
Meprobamate	250	250	100	150	200	167	1450
Chlorpromazine	17	20	2.5	42	150	600	75
Chlordiazepoxide	100	40	2	18	92	150	620

As can be readily seen, the new compound was, across-the-board, more potent than meprobamate and resembled chlorpromazine in many of the tests. In addition, it showed, on further study, a very pronounced taming effect on Rhesus monkeys. The interesting properties of this substance started intensive activity with this, at that time quite unexplored, group of heterocyclic compounds. It resulted in the development in our laboratories of a number of new synthetic approaches and in the synthesis of nearly 1500 benzodiazepines of various types, and about 4000 intermediates.

5. Mechanism of Ring Enlargement

The study on the first method for the synthesis of pharmacologically active 1,4-benzodiazepines, *i. e.* the ring enlargement, suggested the mechanism shown below.

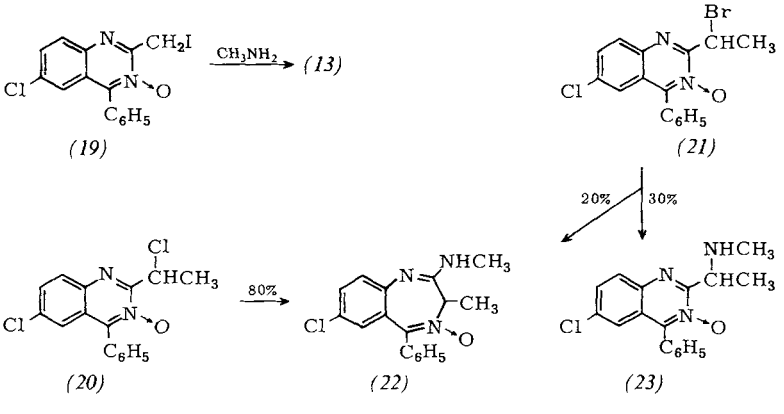


Compound *(12)*, which carries a partial positive charge on C-2 of the quinazoline nucleus, reacts with the nucleophile to form an adduct of structure *(17)*, the reaction being in reversible equilibrium. This adduct in turn, in a concerted reaction, as indicated in formulas *(17)* and *(18)*, undergoes fission between C-2 and N-3, elimination of the chlorine, and formation of a new bond between the exocyclic methylene and the *N*-oxide nitrogen. A short-lived intermediate of structure *(17a)* could also be postulated, which in turn would undergo cyclization to *(14)*. The existence of such an intermediate is suggested by the results of other reactions which will be discussed later.

Further studies showed that we were faced here with two competing reactions, normal substitution and ring enlargement. Good leaving groups, steric hindrance, and substituents in the aromatic nucleus which decrease the positive charge on C-2 led to formation of the normal substitution products. The selection of solvents also affected the course of the reaction. Polar solvents resulted in normal substitution whereas non-polar solvents favored ring enlargement.

5.1. Effect of Leaving Groups[9]

The above effect is well illustrated by the difference in the course of the reaction as determined by the character of the halogen group on the exocyclic methylene group.



The chloromethylquinazoline derivative *(12)* gives, as already mentioned, the ring enlarged benzodiazepine *(14)* in almost quantitative yield. The corresponding iodo derivative *(19)* (obtained readily by treatment of *(12)* with sodium iodide), on the other hand, yields prevalently the normal substitution products *(13)*. The "intermediate" bromo derivative gives, as might be expected, both the normal substitution product *(13)* and the ring enlarged product *(14)*, which were isolated in yields of 30 and 20% respectively. In order to exclude a possible steric effect, caused by the exocyclic methyl group, the behavior of the chloro derivative *(20)* was also studied, and this showed almost quantitative ring enlargement.

In order to obtain comparable data, these reactions were all carried out under identical conditions (methanol as solvent, room temperature, large excess of methylamine). In every case the yields indicate the amounts of isolated crystalline material.

5.2. Effects of Substituents and of Solvents[9]

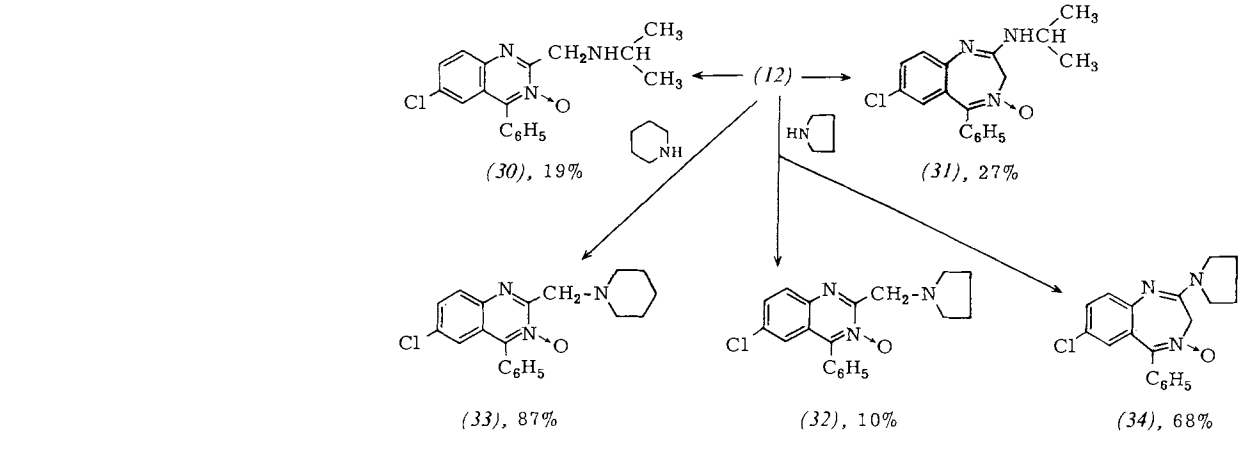
Whereas electron withdrawing substituents (Cl, NO_2, CF_3 *etc.*) on C–6 of the quinazoline nucleus favor ring enlargement, almost to the complete exclusion of normal substitution, electron releasing substituents have the opposite effect. Due to the decrease of the partial positive charge on C–2, the normal substitution offers strong competition, as shown in Scheme 2.

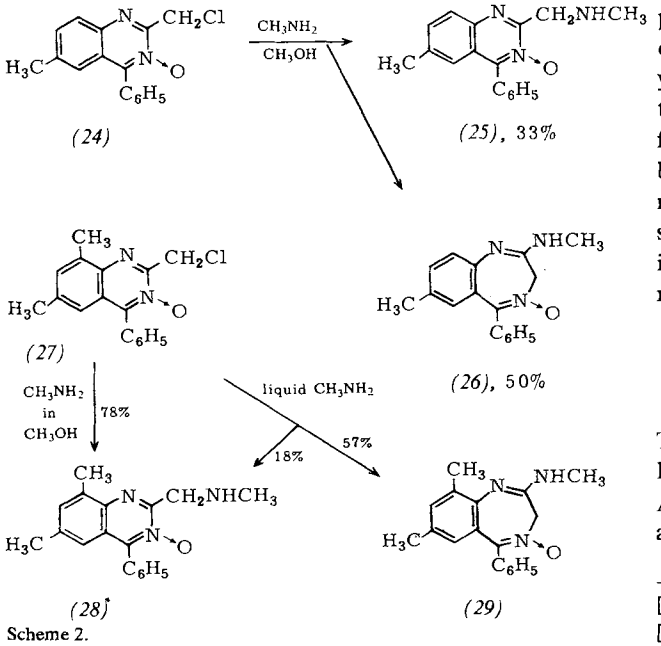
The presence of one methyl group on C–6 of the quinazoline nucleus *(24)* results in the formation of both the normal and the ring enlarged products *(25)* and *(26)*, which were isolated in the indicated yields. Even more pronounced is the additive effect of two methyl groups on C–6 and C–8. The predominant reaction product is the quinazoline 3-oxide *(28)* which is formed in very high yield under standard conditions.

The effect of the solvent is apparent when the reaction is carried out in aprotic liquid methylamine; ring enlargement is highly favored and the main reaction product is the benzodiazepine derivative *(29)*. This course of the reaction is not due to the low temperature as was established by parallel experiments in methanol.

5.3. Steric Effects[9]

The following examples illustrate the influence of sterically hindering substituents on the nucleophile. The bulky isopropylamine causes the formation of both products *(30)* and *(31)*; the even more hindered piperidine[7] results in almost quantitative substitution to yield *(33)*. On the other hand, it is interesting to note that pyrrolidine gives a result which differs considerably from that obtained with piperidine. The ring enlarged benzodiazepine *(34)* is the main reaction product and the normal substitution product *(32)* is formed only to a small extent. This parallels to some degree the difference in the behavior of pyrrolidine and piperidine in enamine reactions.





Scheme 2.

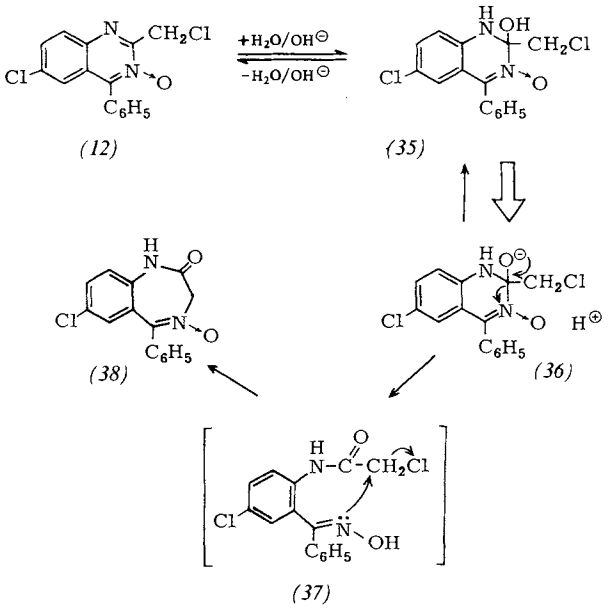
6. Ring Enlargements by Hydroxide Ions

The chloromethylquinazoline 3-oxide *(12)* reacts with hydroxide ions in a manner similar to primary amines. A ring enlargement takes place[10] which results in an almost quantitative conversion to the benzodiazepinone

[9] *G. F. Field* and *E. Reeder*, unpublished results.

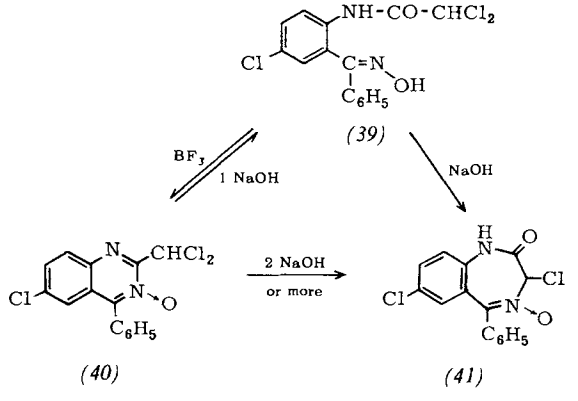
[10] *L. H. Sternbach* and *E. Reeder*, J. Org. Chem. *26*, 4936 (1961).

(38), as shown below. Normal substitution, *i.e.*, replacement of the exocyclic halogen by a hydroxy group was never observed, even with compounds bearing electron releasing substituents in the benzene ring.



This can be explained as indicated above. The first reaction is, in analogy to the reaction with methylamine, addition of OH^- at C–2 of the quinazoline nucleus and formation of the equilibrium intermediate *(35)*. In this intermediate the OH hydrogen has strongly acidic character. This causes immediate ionization to form *(36)*, which cannot revert *via (35)* to *(12)*, but must undergo further reactions, possibly through *(37)*, to *(38)*.

The study of the analogous ring enlargement of the "dichloromethylquinazoline" *(40)*[11] made it plausible that the open compound *(37)* is indeed an intermediate of the reaction *(12)*→*(38)*.



Treatment of *(40)* with 1 mole of alkali yielded the analog of *(37)*, the dichloroacetyl derivative *(39)*, which in this case could be readily isolated. Further treatment of this open compound *(39)* with alkali then gave an excellent yield of the benzodiazepinone *(41)*. Due to the lower reactivity of the chlorines in compound *(39)*, the cyclization to *(41)* does not occur with the speed which made it impossible to isolate the monochloro derivative *(37)* postulated as an intermediate in the preceding reaction. Another indication that in the "monochloromethyl" case the reaction proceeds as formulated is the ease of transformation of the intermediate *(37)* – prepared by unequivocal methods – into *(38)* on treatment with alkali[10].

7. Transformations of Chlordiazepoxide

The interesting biological properties of chlordiazepoxide *(14)* led to intensive study of its chemistry. These investigations were concerned initially with the structure determination [*(14)*→ *(15)*→ *(16)*[7]], but later the study of the effect of structural changes on the pharmacological properties became our main objective[8].

It was found that the readily accessible acetyl derivative of chlordiazepoxide *(14 ac.)* could be converted in excellent yield into the *N*-oxide *(38)*[10] and the simple 5-phenylbenzodiazepin-2-one *(42)*. It was of great interest that the benzodiazepinones *(38)* and *(42)* were pharmacologically at least as active as chlordiazepoxide, as can be seen in Table 2. Hydrogenation of *(42)* in the presence of a platinum catalyst led to a tetrahydro derivative *(43)* with considerably decreased pharmacological activity. This latter finding proved to be a general rule and was confirmed in all cases in which 4,5-dihydrobenzodiazepine derivatives were compared with the corresponding unhydrogenated compounds.

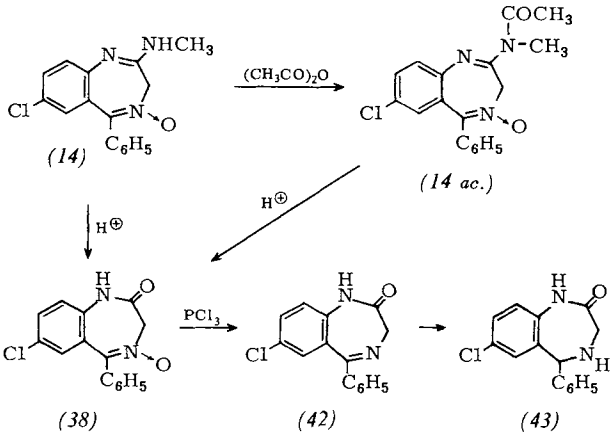


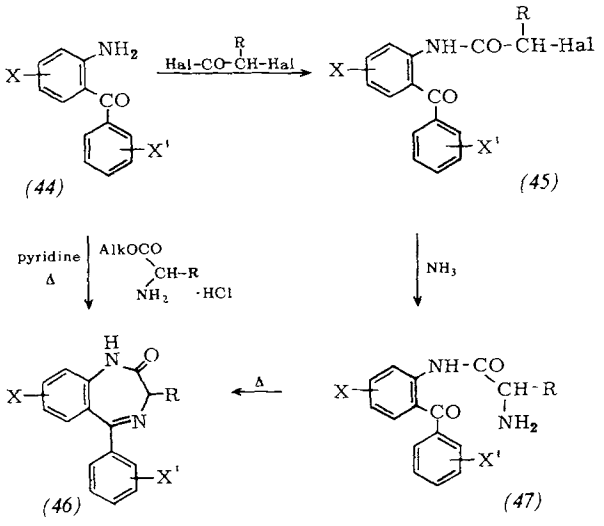
Table 2. Pharmacological properties of a few 1,4-benzodiazepine derivatives.

Compound	Incl. Screen	Fighting Mice	Cat	Anti-Met.	Electroshock Max.	Min.
(14)	100	40	2	18	92	150
(14 ac.)	100	20	2	15	150	150
(38)	75	40	1	6	52	400
(42)	75	20	1	6	25	61
(43)	300	40	10	9.2	36.7	106

8. Methods for the Synthesis of 1,3-Dihydro-1,4-benzodiazepin-2-ones

The benzodiazepine 4-oxides of type *(38)* were relatively readily accessible by treatment of quinazoline 3-oxides such as *(12)* with alkali. This led to a fairly extensive pharmacological investigation of members of this group of compounds bearing different substituents in the phenyl rings.

[11] *A. Stempel, E. Reeder,* and *L. H. Sternbach,* J. Org. Chem. *30,* 4267 (1965).

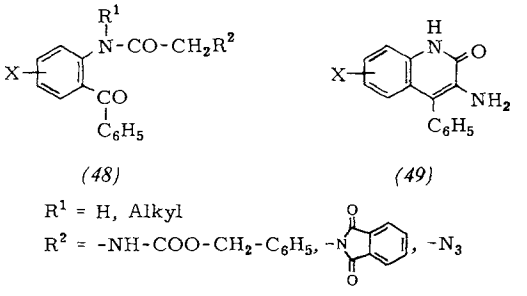


More attractive, however, were benzodiazepinones of type *(42)*, which, as mentioned before, possessed even more pronounced pharmacological activity. Their simple structure induced the search for less involved synthetic approaches and resulted in alternative methods which enabled us to prepare a large number of compounds of this type[12]. The only limiting factor was the accessibility of the 2-aminobenzophenones or 2-aminoacetophenones which were used as starting materials. Our one-step method involves the treatment of an aminobenzophenone *(44)* with glycine ester hydrochloride in pyridine and results in the formation of the benzodiazepinone of type *(46)*, generally in yields of about 50%.

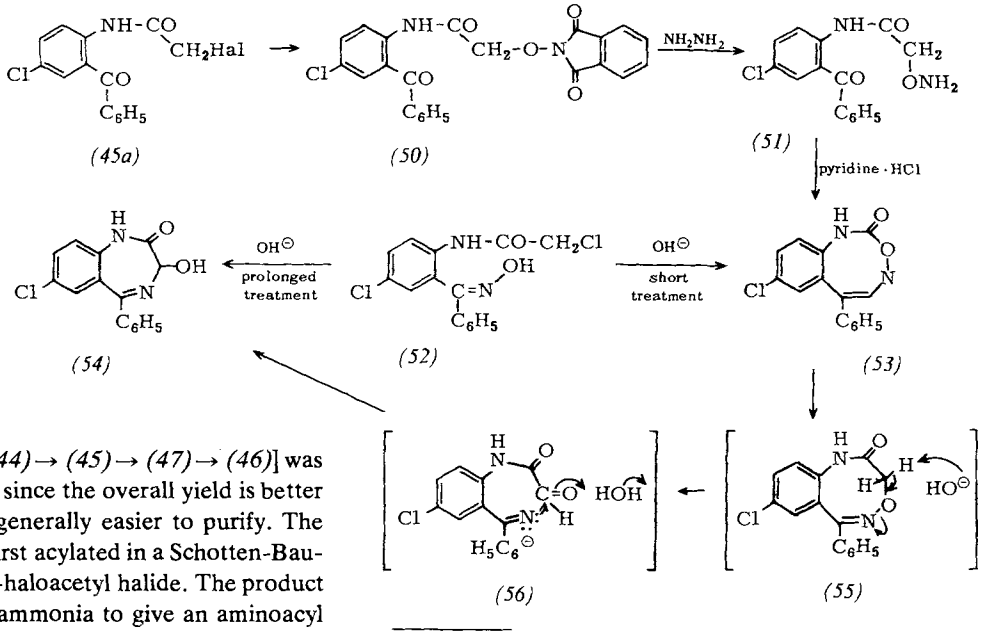
The multistep method [*(44)* → *(45)* → *(47)* → *(46)*] was preferable in most cases, since the overall yield is better and the end-product is generally easier to purify. The aminobenzophenone is first acylated in a Schotten-Baumann reaction with an α-haloacetyl halide. The product of acylation reacts with ammonia to give an aminoacyl derivative which can be readily cyclized. The overall yield in these three steps frequently exceeds 70%. These two methods made the 1,3-dihydro-1,4-benzodiazepin-2-ones the most readily accessible members of this group of heterocyclic compounds.

Another approach used *N*-protected glycine derivatives such as the benzoxycarbonyl[13], the phthaloyl[14] or azido[15] derivatives for the synthesis of intermediates of type *(48)* and the subsequent construction of the seven membered ring.

The ease of formation of this seven membered ring is quite remarkable. Competitive reactions, such as *e. g.* the formation of the aminopyridones[12] of type *(49)* were observed only in rare cases.



Another method for the synthesis of benzodiazepinone derivatives consists in ring contraction of a benzoxadiazocine *(53)*[16a] by treatment with alkali. It leads to 3-hydroxy derivatives such as *(54)*, a class of compounds which was first described by *Bell* and *Childress*[16b][*].



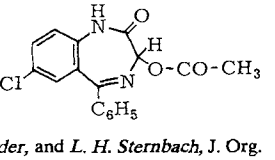
[12] *L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy,* and *A. Stempel,* J. Org. Chem. *27,* 3788 (1962).

[13] *S. C. Bell, T. S. Sulkowski, C. Gochman,* and *S. J. Childress,* J. Org. Chem. *27,* 562 (1962); *A. Stempel* and *F. W. Landgraf, ibid. 27,* 4675 (1962).

[14] Netherlands Patent 6500446 (1966), Delmar; Chem. Abstr. *64,* 5120 (1966).

[15] *J. B. Petersen* and *K. H. Lakowitz,* Acta Chem. Scand. *23,* 971 (1969).

[*] *Bell* and *Childress* used as starting material the *N*-oxide *(38)*, which after subjection to a type of Polonovsky rearrangment and hydrolysis of the 3-acetoxy derivative is converted into *(54)*.

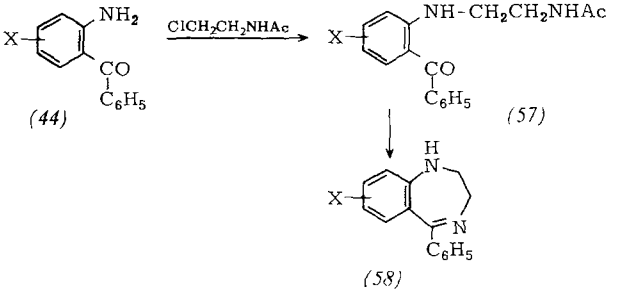


[16] a) *A. Stempel, I. Douvan, E. Reeder,* and *L. H. Sternbach,* J. Org. Chem. *32,* 2417 (1967); b) *S. C. Bell* and *S. J. Childress, ibid. 27,* 1691 (1962).

Two methods for the synthesis of the starting material *(53)* are outlined above. One approach, the transformation of *(50)* and related benzophenone derivatives, *via (51)*, into compounds of type *(53)* served as an unequivocal proof for the structure of *(53)*. Another method consists in the alkali treatment of *(52)* under mild conditions. On prolonged treatment with alkali, compound *(52)* was directly converted into *(54)* in about 60% yield. The mechanism indicated, *via (55)* and *(56)*, explains this transformation. It is interesting to note that under practically the same reaction conditions, the isomeric *anti* oxime derivative *(37)* gives the *N*-oxide *(38)* in excellent yield.

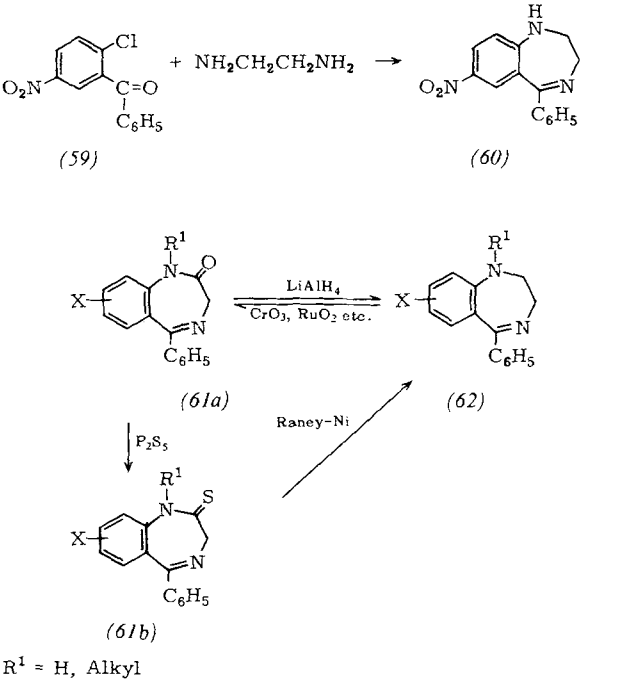
9. 2,3-Dihydro-1*H*-1,4-benzodiazepines

Further studies in the benzodiazepine series led to compounds of type *(58)*. The finding that these products also possessed valuable pharmacological properties resulted in a number of synthetic approaches.



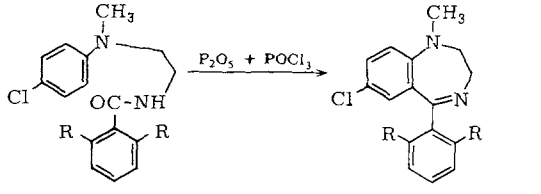
The simplest route consisted in the introduction of the acylaminoethyl moiety into the *o*-aminobenzophenone molecule to yield *(57)*[17], which on hydrolysis gave the desired product *(58)*. The unsubstituted aminoethylamino ketone was not isolated in these cases since it cyclized immediately to form the very stable benzodiazepine derivative *(58)*.

Another method for the synthesis of benzodiazepine derivatives of this type is by reaction of an appropriately substituted *o*-halobenzophenone with ethylenediamine[18]. The yield in these reactions is generally very good. The nitro group in compound *(60)* could be reduced to the amino group, which, *via* Sandmeyer transformations, led to a variety of 7-substituted benzodiazepines. Another method for the preparation of benzodiazepines is the reduction of the 2-one *(61a)* or desulfurization of the thione *(61b)*[17,19][*].



R^1 = H, Alkyl

A Bischler-Napieralski type cyclization proved very useful[21]. This method led in some cases to compounds which were otherwise difficult to synthesize, *e. g.* compound *(66)*[9]. The yields in most cases were very good.



10. 1*h*- and 3*H*-1,4-Benzodiazepines

Compounds of this type are most readily accessible by ring enlargements of 1,2-dihydroquinazoline 3-oxides. In this connection it is amusing to mention how our first dihydroquinazoline *N*-oxide[22] was discovered. At the beginning of our studies when only small quantities of aminobenzophenone oximes were available, attempts were made to recover the last amounts of crystalline material from the oxime mother liquor – which consisted of a dark syrup. A variety of solvents was tried without success. Finally, when in despair we used acetone, a solvent we had previously always gingerly avoided, a large amount of a beautiful yellow crystalline material was obtained, which, however, was quite definitely not the desired oxime.

Closer investigation showed that an unexpected reaction had occurred: the oxime had condensed with the acetone to yield the dihydroquinazoline derivative *(67)*. Further studies showed that the reaction was quite general and that *anti*-oximes of type *(68)* react very readily with aldehydes or ketones to yield dihydroquinazolines[22].

[17] *L. H. Sternbach, E. Reeder,* and *G. A. Archer,* J. Org. Chem. *28,* 2456 (1963).

[18] *L. H. Sternbach, G. A. Archer,* and *E. Reeder,* J. Org. Chem. *28,* 3013 (1963).

[19] *G. A. Archer* and *L. H. Sternbach,* J. Org. Chem. *29,* 231 (1964).

[*] Compounds of type *(62)* could be reoxidized to *(61a)* by various oxidizing agents [20].

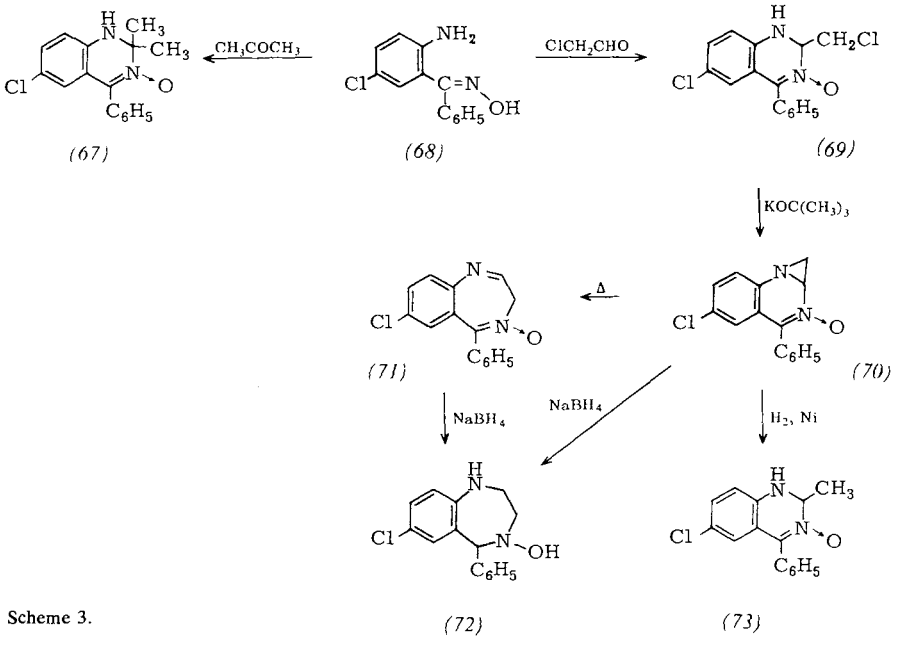
[20] *R. I. Fryer, G. A. Archer, B. Brust, W. Zally,* and *L. H. Sternbach,* J. Org. Chem. *30,* 1308 (1965); *A. M. Felix, J. V. Earley, R. I. Fryer,* and *L. H. Sternbach,* J. Heterocyclic Chem. *5,* 731 (1968).

[21] *H. H. Kaegi,* J. Labelled Compounds *4,* 363 (1968).

[22] *G. F. Field, W. J. Zally,* and *L. H. Sternbach,* J. Org. Chem. *30,* 3957 (1965).

Further study of these compounds showed that dihydroquinazoline derivatives containing exocyclic halogens undergo ring enlargements similar to those studied in the quinazoline 3-oxide series.

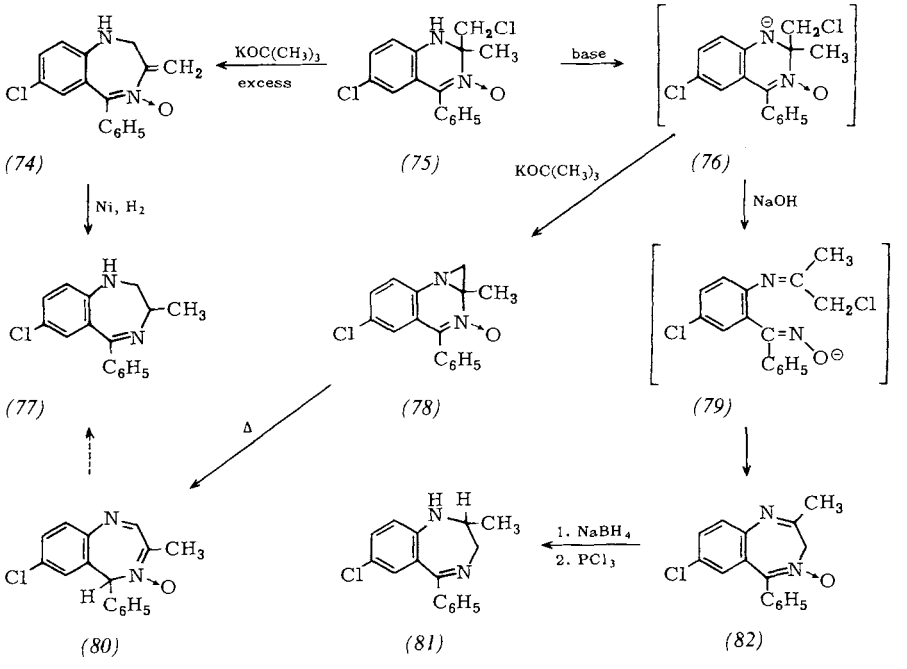
Scheme 3 shows reaction sequences leading to 3*H*-1,4-benzodiazepine derivatives[23]. On treatment of compound *(69)* with potassium *tert*-butoxide the first reaction product is compound *(70)*.



Scheme 3.

The presence of the three-membered ring in *(70)* is shown by the results of reduction experiments. Hydrogenation with Raney nickel as catalyst leads to hydrogenolysis of the bond between the 1-position and the methylene group to yield the 2-methyl-dihydroquinazoline *(73)*. On the other hand, reduction with $NaBH_4$ gave a good yield of the known tetrahydrobenzodiazepine derivative *(72)*. Heating converted compound *(70)* into the valence tautomer *(71)* which could again be reduced in excellent yield to compound *(72)*. The structural assignment for compound *(71)* is based on very convincing spectral evidence (IR, NMR) and is confirmed by the ease of transformation into the known *(72)*.

Investigation of the ring enlargement of a quinazoline 3-oxide *(75)* bearing two substituents on C-2 showed that the course of this reaction depends on the character of the base used and results in the formation of isomeric benzodiazepines. The sequence shown represents an explanation of these reactions. Ion *(76)* is in every case the primary reaction product. If dilute alcohol is used as solvent and sodium hydroxide as base, ring opening occurs to yield a postulated compound *(79)* [similar to *(37)*], which undergoes cyclization to *(82)*. In this reaction sequence the quinazoline *(75)* gives the benzo-



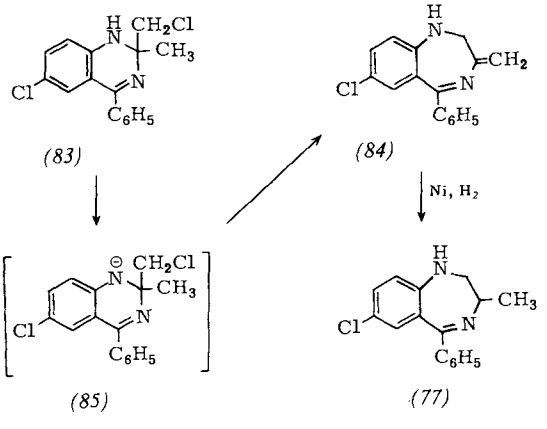
[23] *G. F. Field, W. J. Zally,* and *L. H. Sternbach,* J. Amer. Chem. Soc. *89,* 332 (1967).

diazepine *(82)* (~80% yield), whose structure was indicated by its UV and NMR spectra and confirmed by transformation into the known compound *(81)*.

The reaction of *(75)* with potassium *tert*-butoxide in an aprotic solvent proceeds somewhat differently. The primary reaction product, *i.e.* the ion *(76)*, undergoes intramolecular alkylation to form an aziridino-quinazoline *(78)* whose presence can be easily demonstrated and which on heating transforms into the benzodiazepine *(80)* [*(75)* → *(80)* = 42% yield], the isomer of *(82)*. The structural assignment is based on physicochemical data, UV and NMR spectra (signal for the methyl group) and on the stepwise chemical conversion into the known compound *(77)*.

Ring enlargement of the 2-disubstituted quinazoline 3-oxide under discussion can also take place *via* a third route[9]. When an excess of potassium *tert*-butoxide is used for the protonation of *(75)* an orange compound having an exocyclic methylene group is formed in 25% yield. It has the structure *(74)*. The mechanism of this reaction is not quite clear, but is certainly dependent on the excess of base which abstracts a proton from the exocyclic methyl group. The structure of *(74)* was proved by its NMR spectrum and its transformation by hydrogenation into the known 3-methylbenzodiazepine derivative *(77)*. Thus, three isomers – namely *(74)*, *(80)*, and *(82)* – can be formed on treatment of *(75)* with base.

Whereas the fully aromatic 2-chloromethylquinazolines underwent normal exchange reactions and needed the 3-oxide function in order to undergo ring enlargements, the 1,2-dihydroquinazolines behaved differently[9].

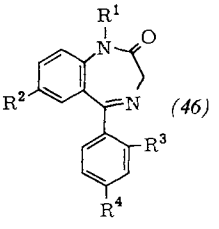


Treatment of *(83)* with a strong base (potassium *tert*-butoxide) resulted again in the formation of an ion of type *(85)*, which then underwent ring enlargement, possibly *via* an oxazirino compound, to yield the benzodiazepine *(84)*. The transformation of *(83)* to *(84)* is relatively clean and occurs with a yield of 60%. The structure of compound *(84)* was established by its physicochemical properties (NMR) and its chemical transformation into the known benzodiazepine derivative *(77)*.

11. Structure-Activity Relationship

Before concluding, a few examples will be given which illustrate some of the rules which could be established in the course of our studies regarding the relation of structure to activity[8].

The 1,3-dihydro-5-phenylbenzodiazepin-2-ones of type *(46)* lent themselves best to these investigations. One reason for this was the ready accessibility of these compounds; more important, however, was the fact that they are the most potent types of benzodiazepines and show,



(46)

Table 3. Pharmacological properties of 1,4-benzodiazepinones.

Cmpd.	R^1	R^2	R^3	R^4	Incl. Screen	Fighting Mice	Cat	Anti- Met.	Electroshock Max.	Min.
(46a)=(42)	–	Cl	–	–	75	20	1	6	25	61
(46b)	CH_3	Cl	–	–	30	10	0.2	1.4	6.4	64
(46c)	–	Cl	Cl	–	100	40	0.1	0.4	13	115
(46d)	–	Cl	–	Cl	>500	>100	–	>800	300	>800
(46e)	–	NO_2	–	–	15	5	0.1	0.5	8.4	132
(46f)	–	CH_3	–	–	>500	>100	–	175	175	>800
(46g)	CH_3	NO_2	F	–	1	0.8	0.02	0.12	12	345

therefore, also the widest variations in activity. They are in this respect more interesting than the 2-amino derivatives of type *(14)*, the tetrahydro-2-ones of type *(43)*, the dihydrobenzodiazepines of type *(62)*, and the last discussed 1*H*- and 3*H*-benzodiazepines.

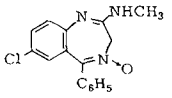
Table 3 shows some compounds of type *(46)* and their pharmacological properties. The substituent on C-7 was found to be of paramount importance, but also substitution on N-1 and in the 5-phenyl ring had a decisive effect on the activity.

Electron withdrawing substituents on C-7 generally imparted high activity, whereas electron donors had the opposite effect.

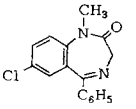
A methyl group on N-1 potentiated the activity, as did a halogen in the *o*-position of the phenyl ring; a substituent in the *p*-position, however, decreased the activity dramatically. The additive character of these effects allowed us to synthesize custom tailored compounds such as, for example, *(46g)* which contained all the features known to impart high pharmacological activity. *(46g)* is indeed the pharmacologically most potent benzodiazepinone known to us.

12. Closing Remarks

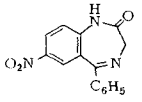
Table 4. 1,4-Benzodiazepines in clinical use.



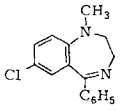
chlordiazepoxide
(Librium®) *(14)*



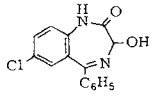
diazepam
(Valium®) *(46b)*



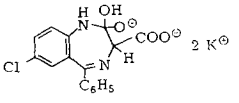
nitrazepam
(Mogadon®) *(46e)*



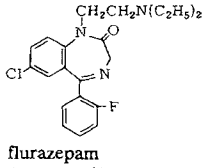
medazepam
(Nobrium®) *(64)*



oxazepam
(Serax®) *(54)*



chlorazepate
(Tranxène®)
(Tranxilium®)



flurazepam
(Dalmane®)

These studies and those of other investigators resulted ultimately in the production of seven 1,4-benzodiazepine derivatives which are now in clinical use as tranquilizers or sleep inducers. Table 4 shows the formulas, the generic names, and also the names of the specialties containing these products.

Additional compounds are being studied and it is to be expected that the number of clinically used 1,4-benzodiazepine derivatives will increase considerably within the next few years.

I wish to acknowledge the dedicated work of my co-workers who contributed so greatly to the development of the chemistry of 1,4-benzodiazepines; in particular, I thank Mr. E. Reeder, Drs. G. Archer, G. Field, R. Ian Fryer, W. Metlesics, G. Saucy, N. Steiger, and A. Stempel. I also want to express my appreciation to the Director of our Pharmacology Department Dr. L. O. Randall and his co-workers for their close co-operation which resulted in the efficient biological evaluation of these compounds.

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Preparative Solid State Chemistry: The Present Position[1,2]

By Harald Schäfer[*]

Dedicated to Professor Wilhelm Klemm on the occasion of his 75th birthday

Two types of reaction are distinguished in solid state chemistry: those in which high mobility of the reactants is aimed at (which can be achieved by the use of high temperatures, by the introduction of defects, by the promotion of surface diffusion, or by means of chemical transport phenomena), and those reactions in which the nature of the products is determined by existing structural elements or lattice defects of the reactants. The importance of paying more attention than hitherto to reaction pathways in preparative solid state chemistry is pointed out.

1. Introduction

The distinction between organic and inorganic chemistry has a historical basis. In some respects it is more meaningful to divide the subject into molecular chemistry and solid state chemistry, a classification that is also useful from the preparative point of view. Theories of reaction mechanism and their practical application are more fully developed in molecular chemistry than in solid state chemistry, for the following reasons:

Molecular chemistry is primarily chemistry in solution. The molecules or ions are so close together in the solution that the diffusion paths (of the order of 10 Å) are of no importance to the course of the reactions, and moreover the diffusion constants are relatively large ($\approx 10^{-5}$ cm^2/sec). Kinetic mechanisms, involving relatively small

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[1] In memory of my late friend *A. D. Wadsley*, of Melbourne, who died on January 7, 1969, and to whom we owe our basic knowledge of the structure relations of the so-called Hägg-Magnéli phases.

[2] Expanded version of an address given at the Colloquium on Preparative Solid-State Chemistry on April 1, 1969 in Aachen (Philips Central Laboratories).

complexes, determine the rate at which such reactions take place, if the latter are thermodynamically possible.

In solid state chemistry the conditions are quite different, especially in the case of reactions between powdered solids: for a reaction between two grains in contact, A + B→AB, the rate is determined by the mobility of the reactants in the solid state. The diffusion paths are long (grain diameter *e. g.* 10^5Å) and the diffusion constants are small. This necessitates the use of high temperatures, and as a rule the products are what one would expect from thermodynamic considerations. In such cases it is not necessary to understand exactly the reaction mechanism in order to achieve a particular aim. Such syntheses appear to be trouble-free:

In the simplest case the solid starting materials, in the form of a mixture of powders or as pellets, are heated sufficiently strongly and for a sufficient length of time for the stable products to be formed. In some cases it may be necessary to conduct the reaction in a sealed tube because of the volatility of one component, but there is no essential difference between this situation and the first.

The preparative procedure so outlined is only the first step for the solid state chemist, and one to which he does not usually give too much attention. The real problem begins with the physical investigation of the product, determination of its crystal structure, its electrical and magnetic properties, light absorption, and so on. This means that more and more work is being published on the physical properties of materials whose early history is either unpublished or unknown.

If any generalization can be made about the work of others, it is that at times one has the impression that the wider development of physical techniques and their increasing claims on the researcher are accompanied by a neglect of the preparative methods.

There is no doubt that many important aspects of the chemistry are lost by the use of such primitive methods of preparation:

a) One cannot control or exploit a reaction without a knowledge of its mechanism.

b) Purely solid state reactions involve no purification effect. Incidental processes (evaporation, reaction with the walls of the vessel) disturb them, because they alter the desired proportions of the reactants in unforeseeable ways.

c) Only in exceptional cases can one obtain single crystals, which are suitable for X-ray structure analysis.

d) Attempts are sometimes made to correct mistakes by the expenditure of much physical and mathematical effort. Since these mistakes arise because insufficient care has been taken in the methods of preparation, such corrections are in principle meaningless.

e) All those compounds which are only stable at lower temperatures are lost.

f) The no less important metastable compounds as a rule remain inaccessible.

In the following we shall examine two limiting cases: the preparation of thermodynamically *stable compounds* by increasing the atomic mobility and the preparation of *metastable compounds* by making use of existing structural elements of the starting materials.

2. Increasing the Mobility of the Reactants

2.1. Solid Diffusion. Defect Concentration

The nature and concentration of imperfections (vacant lattice sites, interstitials, and dislocations) are important factors affecting diffusion in monocrystalline solid materials. The equilibrium concentration of imperfections increases exponentially with rising temperature. In polycrystalline solids diffusion along the grain boundaries must also be taken into consideration.

Pure solid state reactions take place in a finite time if the diffusion constants are at least around 10^{-12}cm^2/sec. This corresponds in principle to Tammann's rule, according to which a useful degree of conversion (*e.g.* in reactions of oxides) will only be obtained if the reactant mixture is so strongly heated that at least one of the components reaches 2/3 of its melting point on the absolute scale.

The concentration of imperfections can be substantially increased by the addition of small quantities of ions with another charge number (doping), but this method is seldom employed for preparation because of the resulting contamination of the materials.

More important is the thermal decomposition of mixed precipitates, solid solutions, or suitable complexes.

Examples:

$(Nb_2O_5, TiO_2, nH_2O) \xrightarrow{T} TiNb_2O_7$ [3] (1)
(X-ray amorphous precipitate)

$(NH_4)_2Mg(CrO_4)_2 \cdot 6\,H_2O \xrightarrow{T} MgCr_2O_4$ [4] (2)

Similarly, spinels MCr_2O_4 were obtained from complexes, where M = Zn, Cu, Mn, Fe, Co, Ni [4]

$(M, Fe_2)(C_2O_4)_3 \quad 6\,H_2O \xrightarrow{T} MFe_2O_4$ [5] (3)
(solid solution)

M = Mg, Ni, Co, Zn, Mn

Thus, for the reaction of a mixture of two oxides (TiO_2 + Nb_2O_5 *etc.*) not only have the diffusion pathlengths been reduced to the order of atomic dimensions, but also many imperfections and large surfaces have been created by the liberation of gaseous decomposition products. This is also true in the case of reactions of solids with gases.

Examples:

The formation of CuO by heating Cu turnings in a stream of oxygen proceeds beyond the Cu_2O stage only very slowly at 1000 °C on account of the considerable length of the diffusion paths through the protective layer. However, CuI changes readily into CuO at 300 to 400 °C in the presence of oxygen[6].

[3] *R. Gruehn* and *H. Schäfer*, Naturwissenschaften *50*, 642 (1963).
[4] *W. Whipple* and *A. Wold*, J. Inorg. Nucl. Chem. *24*, 23 (1962).
[5] *P. Kleinert* and *A. Funke*, Z. Chem. *1*, 155 (1961).
[6] *H. Schäfer* and *M. Rönspiess*, unpublished results (1963).

A similar situation is observed in the case of IrO_2. The oxidation of Ir with O_2 remains quite incomplete at 800 to 1000 °C. In contrast, $IrCl_3$ is completely converted into IrO_2 at 600 °C in a stream of O_2[7].

The reaction of a mixture of $BaCl_2$ and $NiCl_2$ with F_2 (300 °C) leads to a mixture of BaF_2 and NiF_2. On the other hand, $Ba[Ni(CN)_4]$ gives the ternary fluoride $BaNiF_5$[8] on treatment with F_2.

The preparation of $NiPbF_6$ from the oxides PbO and NiO in a stream of F_2 is difficult (if not impossible). However, it proceeds smoothly by the reaction of a mixture of $(NH_4)_2PbCl_6$ and $Ni(NH_3)_6Cl_2$ in a stream of F_2 (on heating from room temperature to 500 °C)[9].

The best way of synthesizing MnF_3 is by the reaction of $(NH_4)_2[MnF_5]$ with F_2 (350 °C)[10].

Seven stable structurally related phases appear at 1300 °C in the NbO_2–$NbO_{2.5}$ system[11,12]. The formation of the respective equilibrium phases takes place more quickly, in a suitable H_2/H_2O atmosphere, the greater the difference in composition (and therefore in structure) between the starting and the final states[12]. This means that the breakdown of one structure and the formation of another proceeds more quickly, because of the available defects and surfaces, than a rearrangement, through solid diffusion. "It is easier to knock an old house down completely and to build a new one, than to achieve the same result by stepwise conversion."

2.2. Surface Diffusion

The phenomenon of surface diffusion is well known through the classic work of *Volmer*[13], who showed that, in the growth of a mercury crystal from the gas phase at low pressures, Hg atoms are first of all adsorbed anywhere on the crystal surface, and reach their final resting place by surface diffusion[14]. Another important contribution was the measurement of the diffusion of benzophenone on glass surfaces[15]. The considerable part played by surface diffusion in the transport of material in finely porous substances has been demonstrated by the work of other authors[16–19]. Today it is well known that surface diffusion plays an important role in adsorption and chemisorption, in crystal growth, in the 'decoration' of crystal surfaces (*e.g.* by the condensation of gold[20,21]) and in heterogeneous catalysis (*e.g.* hydrogen migration on heterogeneous catalysts: "spillover"[22])[23]. However, the part played by surface diffusion in solid reactions has not been consciously emphasized or utilized.

Surface diffusion requires a considerably lower activation energy than solid diffusion, and consequently it is operative at lower temperatures. The diffusion constants for surface diffusion correspond in magnitude to those in solutions and in melts.

Returning to the basic question, let us consider the *thermal decomposition of a solid* with liberation of a gaseous component:

$$AB\ (s) \rightarrow A\ (s) + B\ (g) \qquad (4)$$

Two principal reaction pathways are possible: In the first of these, B splits off leaving the phase AB supersaturated with respect to A; the nuclei of A which are formed at the next step can only grow by *solid diffusion,* since they are in the body of the AB phase and are completely surrounded by it. In the other pathway B splits off from the surface of AB, and the formation and growth of A nuclei take place by *surface diffusion.*

Evidently the second way is frequently decisive, especially if the decomposition takes place not in vacuum but in the presence of a gas phase. As an example we may cite reaction (5):

$$3\ FeOCl\ (s) \rightarrow \alpha\text{-}Fe_2O_3\ (s) + FeCl_3\ (g)\ (^1/_2\ Fe_2Cl_6\ (g)) \qquad (5)$$

The following proposal for the reaction mechanism seems plausible: at a sufficiently high temperature we shall have mobile Fe^{3+}, O^{2-}, and Cl^- ions on the surface of the FeOCl crystal. In this surface film the environment of the Fe^{3+} ions is always changing, with the best possible electrostatic compensation (as in a solution or melt). In this way three Cl^- ions can become attached to an Fe^{3+} ion, and the molecule so formed can escape into the gas phase. As a result of such a process an increased concentration of O^{2-} and Fe^{3+} ions builds up in the surface film which leads, at suitable places, to the formation of nuclei and to the building up of an α–Fe_2O_3 lattice. Obviously such a process must be susceptible to *outside influences* through changes in the composition of the surface film. A good example of this is the thermal decomposition of VI_3[24].

$$VI_3\ (s) \rightarrow VI_2\ (s) + {}^1/_2\ I_2\ (g) \qquad (6)$$

Contrary to thermodynamic expectations, the decomposition of VI_3 takes place at a higher temperature in

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vacuum than under 1 atm. of argon (Fig. 1). This observation can be taken to mean that in the argon atmosphere a certain pressure of iodine vapor builds up over the substance. There will be a corresponding concentration of iodine in the surface film, which will make the vanadium mobile by the chemical transport action of the halogen in the surface film. The steady loss of iodine to the gas phase promotes the formation of nuclei on the surface and thus leads to the building up of the VI_2 lattice.

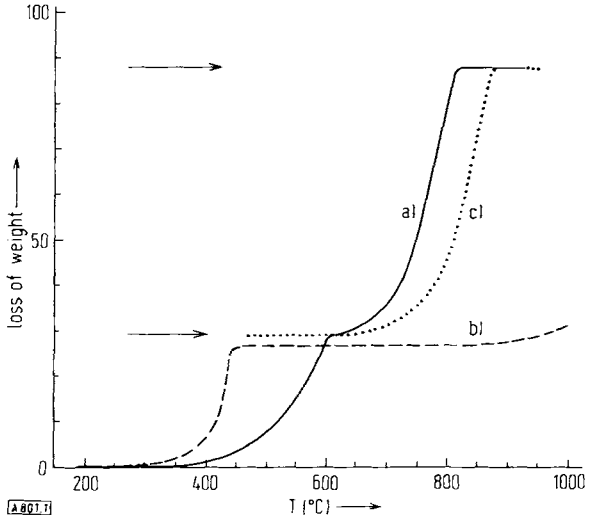


Fig. 1. Decomposition of VI_3 and VI_2 on the thermal balance. Temperature rise 2.7 °C/min. The arrows show the step heights corresponding to the elimination of iodine.

(a) VI_3; vacuum ($< 10^{-3}$ torr), (b) VI_3; 1 atm. of argon, (c) VI_2 (red), well crystallized; vacuum ($< 10^{-3}$ torr).

Comparison of curves (a) and (c) shows further that the VI_2 originating from the VI_3 in vacuum (a) is less well ordered and therefore decomposes at a lower temperature than the well-crystallized material (c).

This reaction mechanism cannot work under vacuum, because the necessary surface film cannot be formed. The thermal decomposition can only proceed rapidly in that case when the solid diffusion is rapid enough, *i.e.* at higher temperatures.

In accordance with this interpretation, it is found from X-ray photographs that the VI_2 obtained in the first case is well crystallized and well ordered, while that obtained by decomposition in vacuum contains many imperfections. In agreement with this, it is also found, on raising the temperature further, that the VI_2 obtained from the vacuum decomposition decomposes at a lower temperature (Fig. 1).

It seems logical to go one step further and to try to influence the composition of the surface film by the *addition of appropriate foreign substances;* in connection with the chemical transport of a solid by a *gas phase,* we must also bear in mind the *mineralizing effect* of the gas phase[25].

Ni recrystallizes strongly when it is heated to about 1000 °C in the presence of a trace of iodine[26], and the same is true for Fe_2O_3[27] in the presence of HCl, and for NbO_2 in the presence of I_2[28].

Up to now these phenomena have been interpreted only as gas-phase transport reactions involving reversible heterogeneous equilibria[25], but we have to remember that surface diffusion with breakdown and build-up of the crystal phases are important steps in normal chemical transport processes over long distances *via* the gas phase. Thus, it seems clear that for the above mentioned mineralizing effect of the transport agent surface diffusion other than *via* the gas phase can also be important.

It is obviously possible to suppress the influence of the gas phase and to isolate the effects of surface diffusion if the reaction is carried out in a *rapid stream of gas.* Consider a system for which chemical transport in the gas phase is possible; if the crystal phase is heated in a rapid gas stream, then the molecules escaping into the gas phase will be carried away without being able to undergo a back reaction on the starting place. Even if this involves considerable recrystallization of the solid phase (which would not happen in the absence of the transporting gas phase at the same temperature) then surface diffusion – *"chemical transport in the surface film"* – must be of decisive importance. A typical example of this is the recrystallization of the Pt catalyst gauze in the industrial combustion of ammonia: platinum is chemically transportable at a temperature of 1000 °C in the presence of oxygen[29] and also in a stream of NO[30]:

$$Pt + O_2 \rightarrow PtO_2\,(g) \qquad (7)$$

$$Pt + 2\,NO \rightarrow PtO_2\,(g) + N_2 \qquad (8)$$

$$PtO_2 \rightarrow Pt + O_2 \qquad (9)$$

Equations (7) and (8) show how the platinum volatilizes (as PtO_2) in the combustion of ammonia. Surface diffusion, *i. e.* chemical transport in the surface film corresponding to equations (7)–(9) is obviously responsible for the extensive recrystallization of the platinum gauze (Fig. 2). During this process the PtO_2 is mobile in the surface film.

Exact investigations of systems in which transport is possible in the surface film but not in the gas phase are of special interest. In this connection we may recall the observation[32] that silver condensed onto graphite recrystallizes readily at room temperature, *if an adsorbed film of water* is present. We may also remember that many reactions that were formerly regarded as typical solid-solid processes are now known to occur at the

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[31] The author is indebted to the Heraeus Platinschmelze Co., Hanau, for the photographs.

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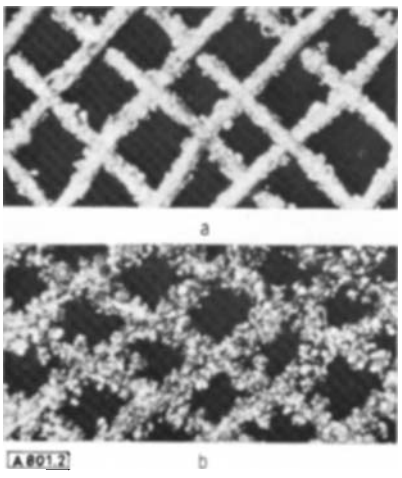


Fig. 2. Platinum catalyst gauze after short (a) and prolonged (b) use in NH_3 oxidation. Diameter of the wire when new 0.06 mm [31].

stated temperatures only if water vapor (and CO_2?) is not excluded. This is true, for example, for reaction (10) at a temperature of 200 °C:

$$2\,BaO\,(s) + 4\,AgI\,(s) \rightarrow 2\,BaI_2\,(s) + 4\,Ag\,(s) + O_2 \quad [33] \quad (10)$$

With respect to the diffusion process surface diffusion can be compared to the processes which go on in the molten state. In fact melts are of great significance for the synthesis of solids and for crystal growth. We need only recall the dissolving power of fluoride melts for oxides. We cannot go further into this wide field in the present article, nor can we enlarge upon the use of small quantities of fluxes as mineralizing agents.

To sum up, considerable preparative advances are made possible by systematic control and utilization of surface diffusion.

2.3. Chemical Transport in the Gas Phase[25]

If *one* of two reacting solid substances is chemically transportable *via* the gas phase by means of a heterogeneous equilibrium this may have important *advantages:*

1) The transformation of solid starting materials into a solid product is usually accompanied by a decrease in volume, which means that the mechanical contact between the reactants becomes worse as the reaction progresses. If, however, the first of the starting materials is mobile by chemical transport, the second will so to speak interact with the 'gaseous solution' of the first:

$$A(s) + B(s) \rightarrow AB(s) \quad (11)$$

$$A(s) + X(g) \rightleftarrows AX(g) \quad (12)$$

$$AX(g) + B(s) \rightarrow AB(s) + X(g) \quad (13)$$

If the reaction product AB is not chemically transportable the solid diffusion of A or B in AB still plays an important role, being as a rule rate-determining. However, because of the transport process the substance A is available for reaction over the whole surface of the B grain, and not only at touching points as in purely solid-solid reactions.

2) The substances A and B will also react, even if they are widely separated, in the presence of a transport agent. This means that it is unnecessary (and usually inappropriate) to use A and B in exactly stoichiometric proportions. The *isothermal* transport ceases automatically when one of the starting materials is used up. It is convenient to use an excess of the transportable material. In this way the synthesis occurs with a selection of materials, and the analysis of the reaction products has some definite significance, in contrast to the case of purely solid state reactions.

Examples:

a) $$2\,CaO + SnO_2 \xrightarrow{900\,^\circ C} Ca_2SnO_4 \quad [34] \quad (14)$$

$$SnO_2(s) + CO \rightleftarrows SnO(g) + CO_2 \quad (15)$$

The formation of Ca_2SnO_4 is markedly accelerated by the addition of CO or H_2, since the SnO_2 can then be transported in the form of SnO(g).

b) $$NiO + Cr_2O_3 \xrightarrow{1100\,^\circ C} NiCr_2O_4 \quad [35] \quad (16)$$

$$Cr_2O_3(s) + 3/2\,O_2 \rightleftarrows 2\,CrO_3(g) \quad [25] \quad (17)$$

In the presence of oxygen, the reaction takes place even if the reactants are separated spatially; in this case the Cr_2O_3 migrates to the NiO.

c) $$11\,Nb + 3\,SiO_2 \xrightarrow{1000\,^\circ C} Nb_5Si_3 + 6\,NbO \quad [36] \quad (18)$$

Nb can be heated in a quartz tube under high vacuum without the thermodynamically favored reaction (18) taking place. On the other hand, if traces of H_2 are present the reaction proceeds to completion: the SiO_2 migrates from the walls of the vessel to the niobium:

$$SiO_2(s) + H_2 \rightleftarrows SiO(g) + H_2O \quad (19)$$

When iodine is used as the transport agent the migration takes place in the opposite direction; the niobium is now transported to the walls of the vessel,

$$Nb + 2\,I_2\,(g) \rightleftarrows NbI_4\,(g) \quad (20)$$

and reacts there with the quartz to form Nb_5Si_3 and NbO[37].

Quartz reacts similarly with tantalum (forming Ta_2Si and Ta_2O_5)[38] and with vanadium (forming V_3Si and VO)[39], if a transport agent is present.

When the reactants are heated to above 600 °C in quartz ampoules, traces of water vapor are liberated from the walls. Often it is these small amounts of water that make the reaction possible, due to their chemical transport action in the gas phase and/or in the surface films. Since the kinetics of the reactions were not generally investigated, we are free to speculate:

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[33] *K. Hardel,* Z. Anorg. Allg. Chem. *357,* 122 (1968).

[34] *S. Tamaru et al.,* Z. Anorg. Allg. Chem. *184,* 385 (1929); *195,* 309 (1931); *206,* 49 (1932).

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[39] *K. E. Spear, P. W. Gilles,* and *H. Schäfer,* J. Less-Common Metals *14,* 69 (1968).

d) The interaction of CdO with VO, V_2O_3, and VO_2 at 700 °C in quartz ampoules[40] leads to the formation of CdV_2O_4, $CdVO_3$ and CdV_3O_7. Additional CdO was introduced into the ampoules in the form of pellets, to compensate partly for the loss of CdO by reaction with the quartz. Since this proved effective, it can only mean that the gas phase is involved in the reaction. Gaseous molecules: H_2O, H_2, Cd; transport of Cd according to equation (21):

$$CdO\ (s) + H_2 \rightleftarrows Cd\ (g) + H_2O \qquad (21)$$

This transport process has already been observed in a temperature gradient[41].

Partial oxygen transport by means of H_2/H_2O has a bearing upon this question of the effectiveness of traces of water. For example, the reaction

$$Nb + NbO_2 \rightarrow NbO \qquad (22)$$

is not perceptible at 900 ° C under high vacuum, but takes place rapidly and completely in a quartz ampoule on the addition of a trace of H_2 or H_2O. The H_2/H_2O gas phase reduces the NbO_2 to NbO and oxidizes the Nb to NbO[28].

There are *additional advantages* if the *reaction product is also chemically transportable*:

3) Solid diffusion no longer plays a part. No troublesome protective layers are formed, because the product is carried away within the temperature gradient. This is also true if one of the starting materials is gaseous; see example (e).

4) The system is then effectively in a state of reversibility. The nature of the starting materials is of little significance, and so the cheapest and most easily available can be used.

5) As a rule single crystals of the product are obtained, without having to take special precautions, and these are at least of a size suitable for X-ray analysis, and are often $\geq$ 1 mm along the edge.

6) Heterogeneous reaction products can often be separated by chemical transport. This is particularly true if one of the products is transported by an *endothermic* reaction and the other by an *exothermic* one. They will then migrate in opposite directions in a temperature gradient.

7) By means of a "buffered gas phase", it is possible to prepare substances of certain desired composition, if complicated phase relationships or homogeneity ranges exist[42].

Examples:

e) Aluminum reacts only very slowly at 800 °C with gaseous sulfur to give Al_2S_3 (quartz ampoule; Al in an Al_2O_3 boat). The liquid aluminum becomes coated with a film of Al_2S_3 which acts as a diffusion barrier. If the same experiment is carried out in the presence of a little iodine and in the same temperature gradient 800 → 700 ° C, then Al_2S_3 separates in large colorless crystals in the 700 °C zone[43]. No Al_2S_3 coating is formed in this case, because the Al_2S_3 is carried away by the iodine.

$$Al_2S_3 + 3\ I_2\ (g) \rightleftarrows 2\ AlI_3\ (g) + 3/2\ S_2\ (g) \qquad (23)$$

It is in the nature of such reversible systems that they tell us nothing about the actual reaction path. Presumably the reaction sequence is:

$$2\ Al\ (l) + 3\ I_2\ (g) \rightarrow 2\ AlI_3\ (g)\ (Al_2I_6) \qquad (24)$$

$$2\ AlI_3\ (g) + 3/2\ S_2\ (g) \rightarrow Al_2S_3\ (s) + 3\ I_2\ (g) \qquad (25)$$

$$2\ Al\ (l) + 3/2\ S_2\ (g) \rightarrow Al_2S_3\ (s) \qquad (26)$$

Analogous relationships are observed if zinc or cadmium are treated with sulfur, with or without iodine as the transport agent[44].

f) Recently it has been observed[45,46] that numerous sulfides (*e.g.* TiS_2, "$VS_{1.7}$", NbS_2, TaS_3, TaS_2, Cr_2S_3, MoS_2, WS_2, FeS_2, CoS_2, NiS_2, PdS, PtS) are chemically transportable under a moderate pressure of sulfur (5–10 atm.), obviously because volatile sulfides are involved. Such processes could play an important, and hitherto unnoticed, role in the synthesis of sulfides from the elements in quartz ampoules.

g) As a further example of the action of small quantities of water vapor (originating *e.g.* from the walls of the quartz vessel), we may consider the reaction of In_2O_3 with W + WO_3 in the temperature gradient (1100 → 1050 ° C)[47]. Here crystals of $In_2(WO_4)_3$ and In_xWO_3 separate out side by side. The gas phase probably contains the molecules H_2O, H_2, In_2O, $WO_2(OH)_2$, and W_3O_9.

h) The possibility of separating the products of a reaction by Taking advantage of the different direction of transport has been referred to several times[25]. Typical examples are shown in Table 1.

Table 1. Chemical transport separations in a temperature gradient.

Deposition product at T_1	at T_2	Temperature gradient (°C) T_1/T_2	Transport agent	Ref.
CrTe	Cr	850/1025	I_2	[25]
Cu	Cu_2O	600/900	HCl	[49]
CuO	Cu_2O	700/800	HCl	[43, 46]
(NbO_2) [48]	NbO	950/1100	I_2	[28]
$Nb_{12}O_{29}$	(NbO_2) [48]	650/750	I_2	[28]
$NbAs_2$	NbAs	850/1050	I_2	[37]

2.4. Comments

There are several different ways of "increasing the mobility of the reactants" in solid state processes, such as *improving the solid diffusion* or *making use of surface diffusion* or of *chemical transport via the gas phase*. The frequently used method of reacting the solid substances

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[42] *H. Schäfer et al.*, unpublished.

[43] *W. Jagusch*, Dissertation, Universität Münster, (1966). See also ref. [25] (English Edition, p. 119).

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[48] The composition of the gas phase is complicated, only a small quantity of NbO_2 being transported. Most of the NbO_2 remains at the starting place.

[49] *H. Schäfer* and *K. Etzel*, Z. Anorg. Allg. Chem. *291*, 294 (1957).

at a sufficiently high temperature is by no means always the best method of synthesis. One should always try, in the synthesis of solids, to understand what course the reaction will follow, as in this way one could learn how to alter this course in a purposeful manner.

3. Influence of Structural Elements of the Starting Material on its Reaction Behavior

In the type of reaction that we have been considering in Section 2, a knowledge of the structure and bonding of the solids is not as a rule very helpful. The thermodynamically stable end-product is obtained because of the increased mobility of the reactants, regardless of the structure of the starting materials. If the structure of the reactants is to have any influence on the course of the reaction and on the nature of the products, then we must avoid giving too large a degree of mobility to the particles – in contrast to the previous type of reaction. This means that we must avoid using excessively high temperatures and must exclude solvent and transport effects. With these conditions, the structure of the starting materials can have a considerable effect upon the reaction:

Structural elements of the starting materials can be taken over into the product (without decomposing in the meanwhile);
the processes which take place at the crystal surface, *e.g.* the formation of nuclei of new phases, can be influenced; lattice imperfections, which may possibly be characteristic for a certain type of structure, can have an effect upon the course of the reaction.

We find ourselves in the domain of *topochemical reactions* in the widest sense. *Pseudomorphs* too belong here, if it is not only the external habit but also the form and structure of the primary crystallite that are influenced by the starting materials.

3.1. Structural Elements of the Starting Material Are Preserved in the Reaction

This basic principle of molecular chemistry has been known for some time in solid state chemistry. We are especially concerned here with *intercalation compounds* in the narrow kinetic sense. The classic case is that of *graphite compounds* which are formed in such a way that the original layers of the graphite structure are preserved, and *e. g.* atoms of potassium or metal chloride molecules of a certain kind are sandwiched between them[50]. This type of reaction is shown also by other layer structures (*e. g.* MoS_2, WS_2[51]). The swelling and cation-exchange capability of certain layer silicates (*e. g.* montmorillonite)[52] are analogous processes. Their behavior can be plausibly explained in terms of the layer-structures of the starting materials. This is also true for intercalation in existing tubular cavities. Intercalation is also known for structures that do not seem quite so predestined for it. New examples of this kind are the *lower oxides of niobium and tantalum* (M_6O, M_4O, M_2O), which are thermodynamically unstable and are formed from the metal and oxygen at a moderate temperature ($< 600°$ C)[53,54]. The oxygen is obviously taken up, and is incorporated into the metal lattice in an ordered manner, with little deformation of the lattice. It is important to notice that the mobility of the oxygens is in this case considerably greater than that of the metal atoms. A similar effect is observed in the case of the higher niobium oxides. The blue-black compounds $Nb_{12}O_{29}$ (corresponding to $NbO_{2.417}$), $Nb_{22}O_{54}$ ($NbO_{2.453}$) and others, all of which are well characterized, are oxidized by air at a relatively low temperature (*e. g.* 650° C) to the colorless Nb_2O_5 without changing their basic structure. The changeover into the stable structure (the high-temperature modification *H*-Nb_2O_5), with the corresponding rearrangement of the niobium atoms, only takes place at a considerably higher temperature ($\approx 1100°$C)[55].

The greater mobility of the oxygen relative to the niobium is unexpected. Normally the smaller cations diffuse much more quickly than the larger anions (compare for example AgI, Ag_2S, Cu_2O, and many scaling processes). One would also expect that to be the case for the higher oxides of niobium, to judge from the ionic radii ($r_{Nb^{5+}} = 0.69$ Å, $r_{O^{2-}} = 1.32$ Å). Possibly the niobium is more firmly fixed than the oxygen on account of its higher charge. Anyway, it is to be assumed that the low-temperature uptake of oxygen by the above oxides of niobium is due to a peculiar, hitherto unexplained, mechanism.

Anderson and *Wadsley*[56] have proposed a model for oxidation and reduction processes which is applicable to compounds with closely related structures derivable from the ReO_3 type. The oxides of the elements W, Mo, and Nb fall into this class. Starting from the ReO_3 structure with its $ReO_{6/2}$ octahedra connected by the corners, it is possible to describe other compounds, not so rich in oxygen, containing blocks of the ReO_3 structure with boundaries in which the octahedra are connected not by the corners but by the edges. The size of the ReO_3 blocks, or the frequency of occurrence of planes with edge-joins (shear planes), determines the composition of the compound. The composition of the whole crystal can be changed in this way, by uptake or loss of oxygen at the crystal surfaces, the shear planes migrating throughout the structure in stepwise fashion, *i.e.* in jumps corresponding to the length of an octahedral edge. The compounds $W_{20}O_{58}$ and WO_3 for example, are theoretically interconvertible in this way. Experimental proof of the model is still lacking.

Experiments with labeled atoms[57] have shown, however, that another mechanism must be even more important: in single crystals of *H*-Nb_2O_5 the oxygen is found to diffuse preferably in a direction parallel to the (mutually perpendicular) shears planes.

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Finally, mention should be made of an as yet incomplete investigation: the oxide-fluorides NbO_2F and TaO_2F, which crystallize in the ReO_3 structure, are found to absorb considerable quantities of HF at slightly elevated temperatures, without losing their single-crystal character[58]. It is to be assumed that the HF goes into the "perovskite holes" of the starting structure. It is unlikely that the HF molecules first adsorbed on the crystal faces themselves migrate into the body of the crystal. More probably the incoming HF molecule displaces an F^- ion from its place in the lattice; and it is this F ion which, along with the H^+, finds its way into the next "perovskite hole". By a repetition of this process, all the perovskite holes could be filled reversibly with HF ("step mechanism").

The most important aspects of this Section have been, of necessity, only roughly outlined. It would be desirable if the available information were critically sifted, and more work done. We should aim at devising a "structural-kinetic" theory, which would predict the relationships between structure and reaction mechanism.

3.2. The Influence of Lattice Defects

The significance of lattice imperfections – especially dislocations – for the kinetic capability of a reaction is illustrated *e. g.* by the classical etch-pit method used to detect lattice defects. The latter can also be important in ordering processes, as shown by the following example: In the thermodynamically stable system of the niobium oxides, seven phases[12] (see Fig. 3) appear at 1300 °C in the region NbO_2–$NbO_{2.5}$. Even at 1300 °C the equilibrium between the crystal phases and the H_2/H_2O gas phase is achieved only slowly (*ca.* 20 h).

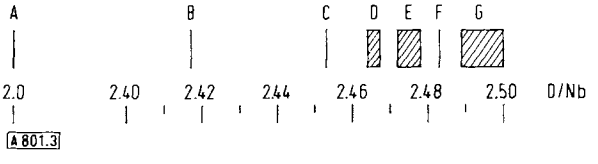


Fig. 3. Niobium oxide phases which are thermodynamically stable at 1300 ° C [12].

All these phases, with the exception of C, can also be obtained at lower temperatures (≈ 1100 °C). The attainment of equilibrium between the crystal phases and the H_2/H_2O gas phase is however strongly retarded at 1100 °C, and it is interesting that this retardation is much more marked in the case of $NbO_{2.5}$ single crystals than in the case of $NbO_{2.5}$ powder (in both cases the *H*-modification).

The reduction of the *powder* leads to the region of phases B to F (Fig. 3), where poorly-ordered material is often obtained. In this way the phase D was first observed[3,59].

The reduction of *single crystals*, in contrast, does not lead to phases in the region B to F, but the single-crystal character remains down to the composition $NbO_{2.44}$[60]. The range of phase G is thus considerably enlarged (metastable, of course). On stronger reduction the lattice breaks down and the NbO_2 phase, which is stable in the presence of the gas phase, is built up.

The single crystals can evidently change their composition, by a still unexplained mechanism, without causing a general rearrangement with formation of the stable phases. In the powder the atoms are much more mobile, a fact that is due not only to the larger surfaces but also to the lattice imperfections.

In this section we must also mention the phenomenon described by *Hüttig*[61] as the *"memory of solid materials"*. According to this, the reaction product "remembers" something about the starting materials, and this memory is manifested in its further reaction behavior. For example, Nb_2O_5 in the T-crystal modification on further heating gives different products, depending upon whether it has been obtained (a) from NbO_2 by oxidation with atmospheric oxygen, (b) from NbO_2 by reaction with chlorine, or (c) by heating of "niobic acid"[55]. Evidently it is sometimes not the ideal structure of the reacting substance, but its characteristic lattice imperfections that represent the true controlling factor of the reaction.

It is clear that we must be careful, in this field, to distinguish between the influence of true structural elements and that of the imperfections.

Turning to materials with distorted lattices one comes across *"active substances"*. Much work in this field has been done by *Fricke* and his associates. These active substances are important because they are especially good starting materials for solid-solid reactions, and also because they can be used to prepare substances that are not otherwise obtainable. A new example of this is the reversible (!) decomposition of "active" Al_2O_3 at 500 °C in vacuum to the black $Al_2O_{2.96}$[62].

4. Concluding Remarks

The solid-state chemist concerns himself at present mainly with structural principles and types of bonding in solids, and their corresponding physical properties. The question of the reaction mechanism is left in the background. Many interesting synthetic pathways are thus left unexplored and unused. The purpose of the present contribution was to point out the unsatisfactory state of affairs, in the hope that these critical reflections will stimulate some action in this direction.

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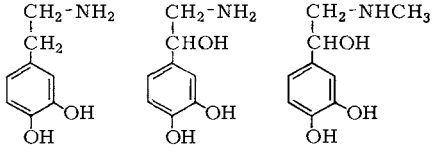
Biochemistry and Function of Biogenic Amines in the Central Nervous System

By Nikolaus Seiler, Lothar Demisch, and Herbert Schneider[*]

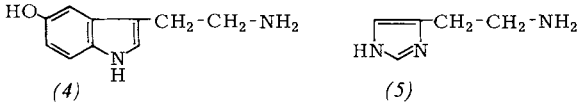
A number of amines are of the utmost importance to the normal function of the nervous system; numerous relationships also exist between certain diseases of the nervous system and the metabolism of these amines. Noradrenaline, serotonin, and histamine are taken as examples to offer some idea of the possibilities and methods of biochemical research that help to elucidate the physiological and pathological processes in the nervous system. The article shows that our knowledge of the functioning of the nervous system, even in a field that has been studied as thoroughly as the transmission of nerve stimuli at synapses, is still in its infancy.

1. Introduction

Biogenic amines are defined as amines that are formed in the course of any metabolic reaction in any organism. This general view, which was advocated *e.g.* 20 years ago by *Guggenheim* in his book on the subject[1], leaves the boundary between the biogenic amines and the alkaloids undefined. During recent years, general interest has been so strongly concentrated on a few particular amines that the majority of the amines present even in the animal organism have receded even farther from the field of view. In most of the publications that have appeared during the past few years, accordingly, only the catecholamines dopamine *(1)*, norepinephrine *(2)*, epinephrine *(3)*, and serotonin (5-hydroxytryptamine; 5-HT) *(4)*, histamine *(5)*, and possibly also acetylcholine are treated as biogenic amines, while *e.g.* the polyamines spermine and spermidine, which are present in nearly



(1) *(2)* *(3)*



(4) *(5)*

all tissues in very much higher concentrations than the catecholamines[2,3], as well as simple β-phenylethylamines, indolamines, and aliphatic monoamines and diamines are often completely ignored. This is because the great importance of catecholamines and serotonin to many physiological functions is already known, whereas our knowledge about the functional importance of other amines has many gaps or is totally inadequate.

The work carried out in recent years has been directed mainly toward the investigation of the function of the amines in the central nervous system. In this article, which will be confined to the amines in the central nervous system, we shall be concerned almost exclusively with dopamine, norepinephrine, serotonin, and histamine, and only these will be covered by the term "biogenic amines". Acetylcholine, in spite of its outstanding importance, must be omitted from our discussions, which would otherwise cover too wide a field. There has, however, been a recent trend back to the broader use of the term "biogenic amines". This is partly because sufficiently sensitive methods have been available for a long time for the detection of the catecholamines, serotonin, histamine, and acetylcholine, whereas the methods required for a successful experimental investigation of the other amines were largely lacking.

2. Methods of Detection and Determination

The concentration of the biogenic amines in the brain, as in most organs, is very low. It can be seen from Table 1 that it is generally less than 1000 ng/g of moist tissue. This means that very sensitive analytical methods are required for their determination, particularly since the quantities of tissue available are usually limited.

Some methods make use of the biological actions of the amines, *e.g.* their action on the blood pressure or on the contraction of smooth muscle (uterus, small intestine). These methods are characterized by high sensitivity, and the biogenic amines (catecholamines, serotonin, histamine, acetylcholine) were discovered with their aid. However, it is difficult to distinguish between different substances having a similar action by biological methods, and these methods have therefore been replaced over the years by more specific chemical methods. For this

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reason, the biological methods will not be discussed in detail, and the reader is referred instead to comprehensive descriptions elsewhere[4,5].

2.1. Nonspecific Methods for General Use

Color reactions or coupling with colored or fluorescent molecules generally allow the use of optical methods for the determination of amines. The most commonly used reagents are still Ninhydrin for primary and secondary amines and the Dragendorff reagent for secondary and tertiary amines[6,7]. However, the scope of these colorimetric methods is limited by their relatively low sensitivity. Nevertheless, *Perry et al.*, for example, were able to identify a series of amines in tissues and excreta by a combination of ion-exchange chromatography and two-dimensional paper chromatography with Ninhydrin for staining[8–12]. *Honegger* used thin layer electrophoresis for the separation of brain amines[13].

As in the analysis of amino acids, numerous coupling reagents that form colored reaction products with primary and secondary amines have been suggested[14–23]. The most important of these reagents is 2,4-dinitrofluorobenzene (DNP-F), which forms yellow derivatives with amines. After separation by column chromatography, the amines are treated with DNP-F as described by *Dubin* and determined spectrophotometrically[24]. The DNP derivatives can be detected on chromatograms in quantities as small as 5 nmole.

It was found that the detection sensitivity could be increased by a factor of about 100 by the use of 5-dimethylaminonaphthalene-1-sulfonyl chloride (DANS-Cl)[25] and of 4-chloro-7-nitrobenzol[*c*]-[1,2,5]oxadiazole (NBD-Cl)[26] as coupling reagents. [^{131}I]-*p*-Iodobenzenesulfonyl chloride (pipsyl chloride) has also been used for the determination of histamine[27]; the resulting derivatives can be detected even in small quantities because of their radioactivity.

The detection methods described so far are nonspecific by their nature, in that they merely show the presence of a sufficiently basic primary or secondary amino group in a molecule. Moreover, most of the reagents mentioned also react with phenols. They can be used to advantage only if the mixture of amines (*e.g.* from a tissue extract) or of their derivatives can be separated.

All the usual chromatographic and electrophoretic techniques, particularly paper and thin layer chromatography, have been used for the separation of the amines. Thus *Lockhart* separated the DNP derivatives on paper chromatograms[28], while *Parihar et al.*[29] and *Zeman* and *Wirotama*[30] separated them on thin layer chromatograms. *Seiler* and *Wiechmann* have described systems for the separation of many DANS-amides by thin layer chromatography[31–33]. DANS derivatives can also be successfully separated on paper[34,35]. *Reisch et al.* have recently separated a number of NBD derivatives by thin layer chromatography[36]. The DNP and DANS derivatives are very well suited for the mass-spectrometric identification of the amines[30,37–40].

Since the general methods described so far have only occasionally been used specially for the determination of the catecholamines, serotonin, and histamine, no details will be given here. It is appropriate, however, to point out that the problem of the quantitative determination of colored or fluorescent substances separated by thin layer or paper chromatography has been solved in principle[41–44].

2.2. Gas Chromatography

Though the technique of gas chromatography is very highly developed, this method has not been widely used for the determination of biogenic amines. The gas chromatography of the free amines is obviously associated with special difficulties[45,46].

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The detection of the trimethylsilyl ethers of the catecholamines with flame ionization detectors has proved to be relatively insensitive[47–49]. The best method appears at present to be the separation of the trifluoroacetyl derivatives of the biogenic amines in a capillary column combined with an electron capture detector or by direct coupling of the gas chromatograph and the mass spectrometer and recording of the total ion current[50–52]. The gas chromatographic separation of DNP amines was recently also described[53].

2.3. Mass Spectrometry

The high sensitivity and the separating power of the mass spectrometer are utilized by *Boulton* and *Majer* for the determination of amines in crude tissue extracts[54]. In this method, the integrated ion current of the molecule-ion is measured under standardized conditions (integrated ion current technique).

2.4. Specific Fluorometric Methods

By far the majority of the investigations on the distribution and metabolism of the biogenic amines were carried out by methods that made use either of the fluorescence of serotonin at certain pH values or of special reactions of the amines with formation of fluorescent derivatives[55]. The determination of serotonin in the brain and other tissues by measurement of the fluorescence of this amine in 3N HCl at 550 nm is due to *Bogdansky et al.*[56]. *Jepson* and *Stevens*[57] were the first to observe that serotonin reacts with Ninhydrin to form an intensively fluorescent product. *Vanable*[58], and later *Snyder et al.*[59], used this reaction as the basis of specific determination methods that are eight times as sensitive as *Bogdansky*'s method. According to *Snyder et al.*, the detection sensitivity of the method is 10 ng of serotonin. In more recent variants of these methods, only the extraction and separation methods have been changed, and the technique of the fluorescence measurement has been improved[60–63].

The fluorescence of the catecholamines in acidic solution is too nonspecific to be used for their determination in the brain, and is used only for the measurement of the total content of catechol derivatives in adrenals[64]. The determination of the catecholamines is based on two principles, *i.e.* conversion into trihydroxyindole derivatives (adrenolutin and noradrenolutin) and condensation with ethylenediamine. The trihydroxyindole method appears to be the more specific. Numerous oxidizing agents used under various reaction conditions have been suggested for the oxidation of the catecholamines[55, 65]. The most important at present are $K_3[Fe(CN)_6]$ and iodine. With potassium hexacyanoferrate (III), norepinephrine and epinephrine can both be oxidized at pH = 6.5, and epinephrine alone at pH = 3.5, whereas dopamine, 3-*O*-methylnorepinephrine (normetanephrine), and 3-*O*-methylepinephrine (metanephrine) do not react under these conditions[66]. On oxidation with iodine, dopamine is also converted into a lutin, and can be determined in the presence of norepinephrine and epinephrine on the basis of the different activation and fluorescence maxima[67–69]. The 3-*O*-methyl derivatives of the catecholamines can also be determined by the trihydroxyindole method[70,71].

The ethylenediamine method is based on the work of *Weil-Malherbe*[72–74] and of *Harley-Mason* and *Laird*[75]. The course of the condensation reaction has not yet been entirely elucidated[55]. The condensation products of epinephrine and norepinephrine can be distinguished by their different fluorescence maxima. This method is also suitable for the determination of dopamine[76], and has been used for the detection of the catecholamines on chromatograms[7].

Methods used for the concentration and separation of the catecholamines include extraction[77,78], adsorption on Al_2O_3[79], and above all chromatography on cation exchange columns[80,81]. The number of variants published in recent years, which relate not only to the concentration and separation, but in particular also to the stabilization of the lutins with ascorbic acid[55], sodium sulfite[82], sodium tetrahydridoborate[83], dimercaptopropanol (BAL)[84], and other antioxidants, as well as to the conditions of the oxidation and of the condensation with ethylenediamine, is so large that *Häggendal* stated in his review[81] that practically every laboratory concerned with catecholamine determinations appears to have developed its own method.

The catecholamines can be determined fluorometrically in the nanogram range by using smaller volumes and microcells. The

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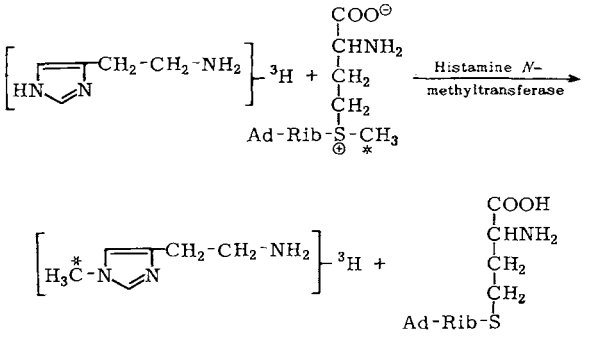
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most recent efforts have been aimed at the determination of as many amines as possible in a single sample of tissue[85–88] and the automation of the methods [89–91].

The fluorometric determination of histamine is nearly always preceded by condensation with phthalaldehyde as described by *Shore et al.*[92]. The fluorescent product of this reaction has not yet been definitely identified. Histidine, spermidine, and other substances[93] also give fluorescent derivatives with phthalaldehyde. Due consideration was not given to this point in very many determinations of histamine in the brain and other tissues, and the results obtained in earlier histamine determinations were consequently much too high. This also made failure inevitable in the attempted histochemical demonstration of histamine in brain sections with phthalaldehyde. The only value of the method was for the demonstration of histamine in the mast cells of the small intestine, where it is present in very high concentrations[94, 95]. The method first reported by *Kremzner* and *Wilson*[96] for the separation of interfering substances by ion exchange chromatography has been improved to such a degree in recent years[97–100] that as little as 25 ng of histamine can now be reliably determined.

2.5. Radiochemical Methods

A specific enzymatic method for the determination of histamine has been developed by *Snyder, Baldessarini,* and *Axelrod*[101]. A small quantity of [^{3}H]-histamine and *S*-adenosylmethionine having a ^{14}C-labeled *S*-methyl group are added, together with



Scheme 1. Radiochemical determination of histamine. Ad-Rib = adenosyl.

histamine *N*-methyltransferase, to the tissue sample. The enzyme converts histamine specifically into [1-^{14}C]-methyl-4-histamine (Scheme 1). The ^{14}C/^{3}H ratio in the extracted methylhistamine is directly proportional to the quantity of histamine in the tissue sample. As little as 2 ng of histamine can be detected in this way.

The method devised by *Engelmann et al.*[102] is also based on the same principle of enzymatic labeling and measurement of the ^{14}C/^{3}H ratio; in this case, the ^{14}C-labeled *S*-methyl group from *S*-adenosylmethionine is transferred to the 3-OH group of the catecholamines by catecholamine *O*-methyltransferase (COMT) (see Scheme 2). *Franklin* and *Majer*[103] added [^{14}C]-catecholamines to the samples and then acylated the hydroxyl groups with [^{3}H]-acetic anhydride. After separation of the labeled products, the ^{3}H/^{14}C ratio is determined. The advantage of the double labeling methods is that the isolation and purification of the substances to be determined need not be quantitative, since the isotope ratio is a direct measure of the quantity of the substance that was present in the tissue. Any desired number of purification steps may therefore be included.

The rate of the enzymatic [^{14}C]-*N*-methylation of norepinephrine by phenylethanolamine *N*-methyltransferase is utilized by *Saelens et al.*[104] for the specific quantitative determination of norepinephrine in the presence of physiological concentrations of the other catecholamines.

2.6. Histochemistry

The conversion of indole derivatives into the intensely fluorescent β-carbolines by condensation with formaldehyde in the presence of acid has been in use for a long time in *Procházka*'s reaction[105] for the detection of indoles on chromatograms. A series of ring-substituted β-phenylethylamines can also be converted into fluorescent isoquinoline derivatives by condensation with formaldehyde[106].

As was first observed by *Falck* in 1962, the condensation of the catecholamines and of serotonin with formaldehyde gas proceeds even under very mild conditions in the presence of proteins or certain amino acids, with formation of intensely fluorescent 3,4-dihydroisoquinolines or the β-carboline deriva-

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tive[107,108]. The reaction products are partly bound to the proteins, possibly *via* methylene bridges, so that they cannot be extracted with organic solvents. These observations formed the basis of the method that has been used with outstanding success over the last eight years for the cellular localization of the catecholamines and of serotonin in tissue sections. The method has been described in detail by *Falck* and *Owman*[109] and by *Corrodi* and *Jonsson*[110]. It is possible to distinguish norepinephrine, dopamine, and serotonin in the cells by measurement of the excitation and fluorescence spectra of the formaldehyde condensation products with the aid of a microspectrofluorometer[111–115]. Treatment of catecholamines and indolamines with formaldehyde gas also allows the detection of these substances on silica gel G layers[116,117].

3. Metabolism

3.1. Biogenesis

It can be seen from Schemes 2–4 that the reactions that lead to the formation of the biogenic amines and that cause their degradation or physiological inactivation in the mammalian organism are formally identical for the catecholamines, serotonin, and histamine. They involve biosynthesis by decarboxylation of the corresponding amino acids, and inactivation by oxidation and methylation. All the enzymes associated with the metabolism of the biogenic amines have been detected in the brain[118].

For the biosynthesis of dopamine and serotonin, the immediate precursors of the amines *i.e.* L-3,4-dihydroxyphenylalanine (dopa) and L-5-hydroxytryptophan (5-HTP), must first be produced by hydroxylation of tyrosine and of tryptophan. The hydroxylation appears in both cases to be the rate-determining step of the reaction sequence, which is inhibited by the final products (feedback), and so regulates the catecholamine and serotonin syntheses[119–127].

Tyrosine hydroxylase can use only L-*p*-tyrosine as the substrate. Fe^{2+} and tetrahydropteridines act as cofactors[127]. On the other hand, tryptophan hydroxylase, which also requires Fe^{2+} and tetrahydropteridines as cofactors, is a relatively unspecific enzyme, and can hydroxylate several aromatic amino acids in the benzene ring. However, the enzyme isolated from brain, unlike that from peripheral organs, cannot convert phenylalanine into tyrosine[128–130].

Dopa and 5-hydroxytryptophan are decarboxylated in the brain by the same enzyme to the corresponding amines, as has been shown by numerous observations. Dopa decarboxylase, which was first detected in kidney by *Holtz*[133], is not very specific, so that in addition to 5-hydroxytryptophan and dopa, a number of other aromatic amino acids, *e.g. o-* and *m*-tyrosine, are suitable substrates for the enzyme from brain. The enzyme requires pyridoxal 5-phosphate as a cofactor[134, 135]. The decarboxylation of the amino acids cannot be the rate-determining step of the amine biosynthesis, since the reaction rate is 75 times as high for dopa decarboxylase as for tryptophan hydroxylase[132]. Though histidine can also be decarboxylated by the unspecific decarboxylase for aromatic L-amino acids[134], there is still no agreement as to whether the histamine in the brain is formed physiologically by this or by a more specific enzyme[136].

The final step in the biosynthesis sequence of norepinephrine is the hydroxylation of the ethylamine side chain of dopamine by dopamine β-hydroxylase. The hydroxylation proceeds in the presence of ascorbic acid and oxygen[140]. In addition to dopamine, many other β-phenylethylamines are converted into β-hydroxy derivatives by this enzyme[141].

The distribution of the hydroxylases and of the decarboxylases in the various regions of the brain is substantially similar[131]. The highest dopa decarboxylase and histidine decarboxylase activities were found in the nucleus caudatus, the putamen (corpus striatum), and the hypothalamus[137–139]. The topographic distribution of the amines also corresponds in general to the distribution of the enzymes that synthesize them. However, norepinephrine is a striking exception. Whereas a high dopamine β-hydroxylase activity can be detected in the corpus striatum *in vitro*[142], only a little norepinephrine is found in this region together with a large quantity of dopamine (cf. Table 1 and Fig. 1). The *in vivo* activity of the hy-

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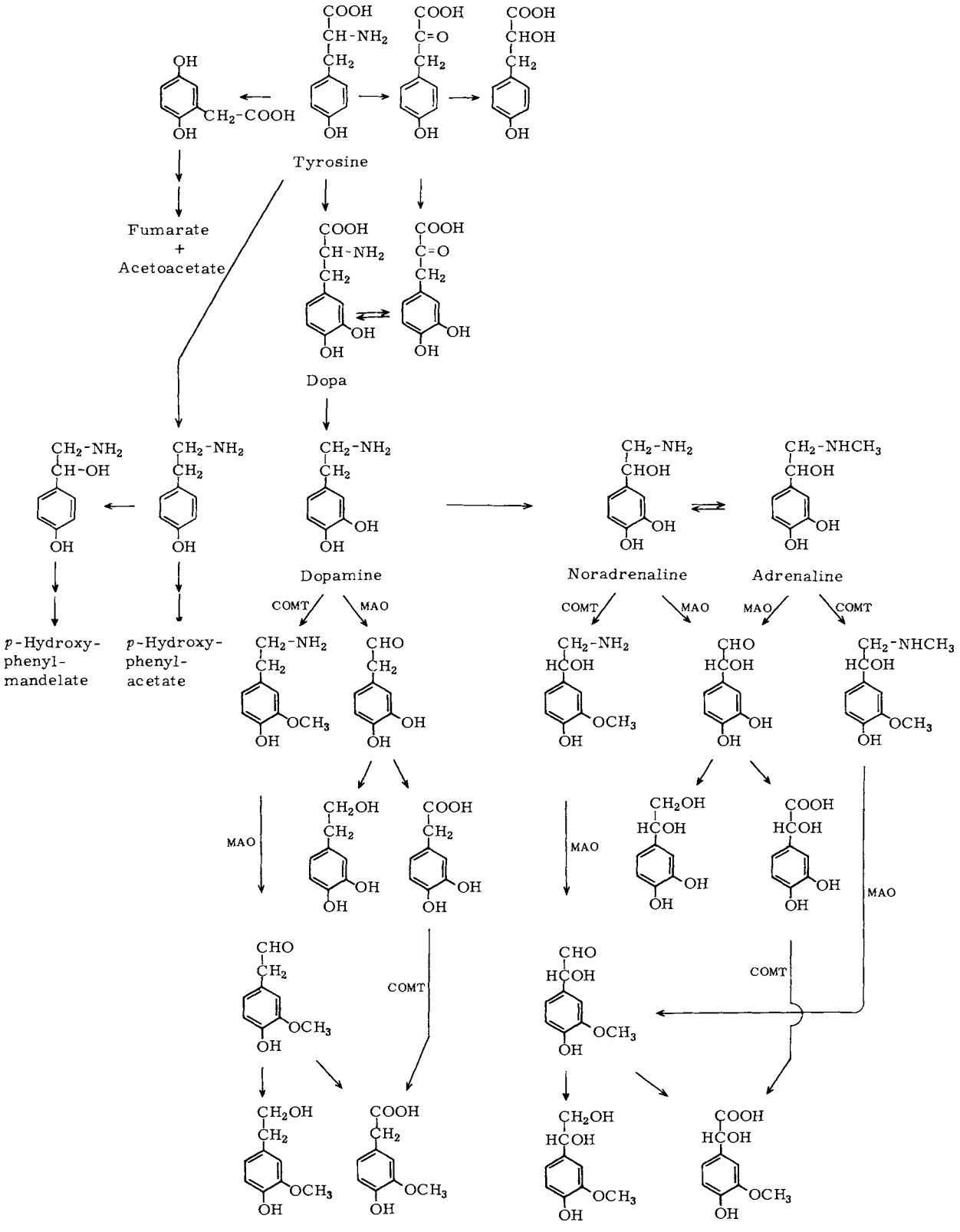
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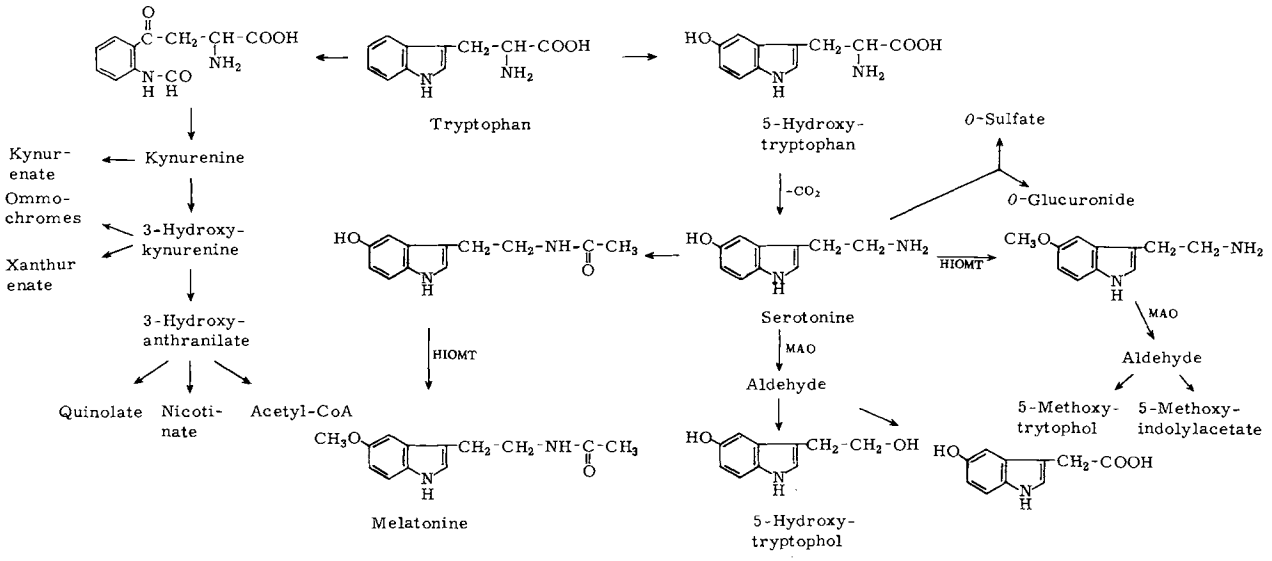
droxylase must therefore be low in the corpus striatum. This means that either the dopamine and the enzyme are located in different metabolic compartments of the cells of the corpus striatum, or cofactors that are essential to the full activity of the β-hydroxylase are absent from these cells[143, 144].



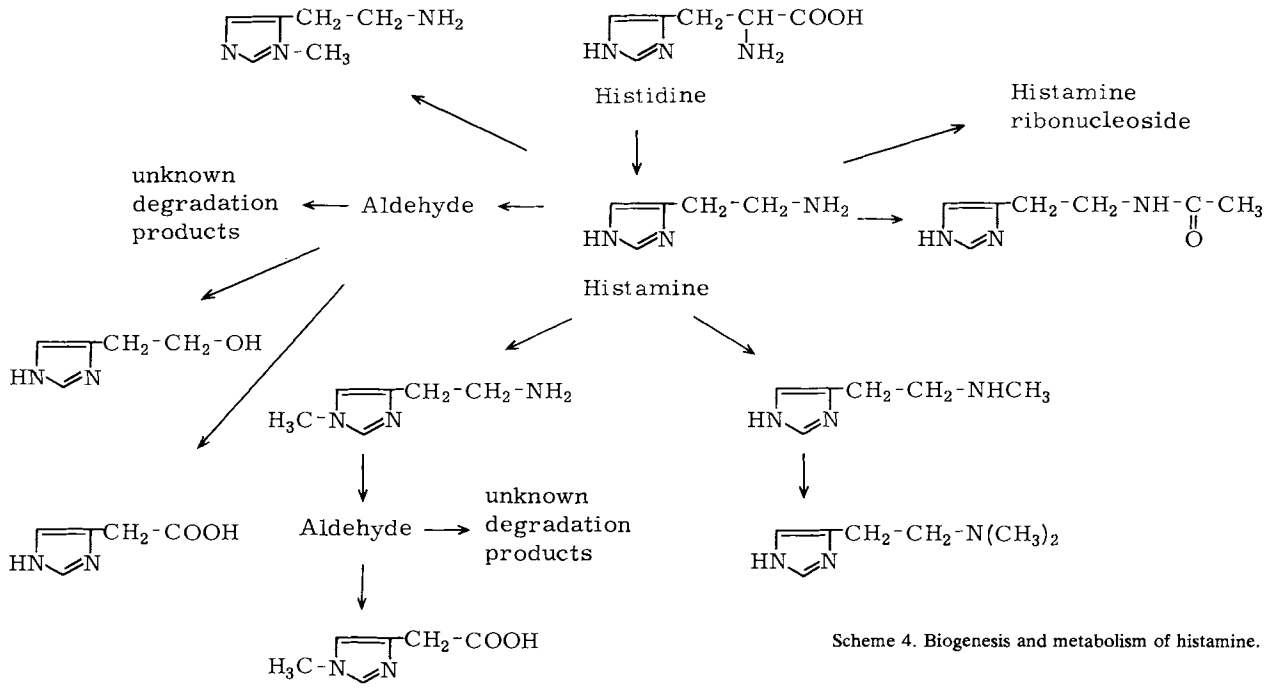
Scheme 2. Biogenesis and metabolism of dopamine, norepinephrine, and epinephrine. MAO = monoamine oxidase, COMT = catecholamine *O*-methyltransferase.

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Scheme 3. Biogenesis and metabolism of serotonin. MAO = monoamine oxidase, HIOMT = hydroxyindole *O*-methyltransferase.



Scheme 4. Biogenesis and metabolism of histamine.

Table 1. Topographic distribution of the biogenic amines in the brain (dog or cat). Concentrations in ng/g of moist tissue weight [143, 258, 259] (see also Fig. 1).

Brain region	Acetyl-choline	Dopamine	Noradren-aline	Sero-tonin	Histamine
Bulbus olfactorius	1300	<100	<100	<100	<100
Neocortex	2000	<100	<100	300	<100
Cornu ammonis		<100	<100	900	<100
Corpus striatum	3000	9900	<100	700	140
Thalamus,	3000	<100			
medial region			240	500	250
ventrolateral region			80	0	75
Hypothalamus	1900	250			
Corpora mamillaria			410		1150
ventral region			900		800
dorsal region			400		480
preoptic region			280		430
Substantia nigra					
pars compacta		760			
pars reticularis		340			
Tegmentum	1600	200	370	1000	200
Cerebellum	200	<100	<100	<100	0
Area postrema			1040	260	920
Pituitary, anterior					2400
posterior					1700
Pituitary stalk		1300		1400	5200

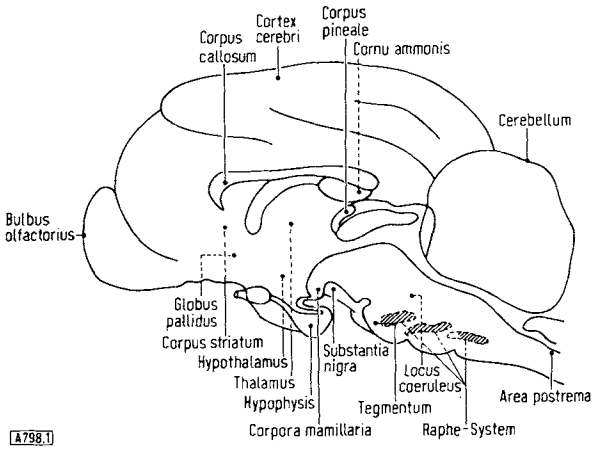


Figure 1. Median view of the right-hand half of the brain of the cat. The parts and regions of the brain mentioned are indicated by continuous lines when they lie in the plane of the section, and by broken lines when they lie behind the plane of the section.

Owing to the great practical difficulties, opinions differ as to the quantity of epinephrine that is present in the central nervous system, which is very small in any case. On the other hand, the enzyme that methylates norepinephrine to form epinephrine, *i.e.* phenylethanolamine *N*-methyltransferase, has been definitely detected in the brain. The methyl group donor in this reaction, as in many biological methylations, is *S*-adenosylmethionine[145]. Epinephrine can also be demethylated to form norepinephrine.

3.2. Degradation

According to the current view, catecholamines liberated from the nerve cells by nerve stimuli or by substances having a sympathomimetic action are physiologically inactivated either by an active re-uptake mechanism or by 3-*O*-methylation[146]. Catecholamine *O*-methyltransferase (COMT) transfers the methyl group of *S*-adenosylmethionine onto a series of catechol derivatives, the ratio of 3- to 4-*O*-methylation being strongly dependent on the structure of the side chain of the catechol derivative[147]. The 4-*O*-methylation plays only a very minor part *in vivo*.

Histamine is also methylated to a large extent on N-1 in the brain (cf. Scheme 4)[148, 149], whereas the physiological inactivation of serotonin by methylation is of no importance. On the other hand, the methylation of *N*-acetylserotonin by *N*-acetylserotonin *O*-methyltransferase in the pineal body is an important step in the synthesis of melatonin (cf. Scheme 3)[150].

The second path for the physiological inactivation of the amines, *i.e.* oxidative deamination by amine oxidases, leads first to the aldehydes, which cannot generally be detected directly. These are then either dehydrogenated to form the acids or reduced to the alcohols. The phenylacetic acids are generally formed preferentially from β-phenylethylamine derivatives, and the ethylene glycols from β-phenylethanolamines. The main product of norepinephrine metabolism found in the brain is accordingly 4-hydroxy-3-methoxyphenylethylene glycol, which was detected in the form of its 4-*O*-sulfate[151], whereas the norepinephrine in peripheral organs is mainly converted into 4-hydroxy-3-methoxymandelic acid (cf. Scheme 2). Dopamine is oxidized in the brain and in the peripheral organs to homovanillic acid (4-hydroxy-3-methoxyphenylacetic acid) and to 3,4-dihydroxyphenylacetic acid. There is evidence that the 3,4-dihydroxyphenylacetic acid is formed first, and is later 3-*O*-methylated[152, 153]. However, 3-methoxytyramine has also been detected in the brain, so that part of the dopamine can undoubtedly also be inactivated by direct methylation[143, 154].

Norepinephrine as well as dopamine is degraded, mainly by oxidation, in the corpus striatum[144]; the dopamine-rich cells of the corpus striatum differ very clearly in this respect from the nerve cells of the cerebral cortex.

In addition to 5-hydroxyindolylacetic acid, a small quantity of the corresponding alcohol, 5-hydroxytryptophol, is also formed from serotonin (cf. Scheme 3)[155, 156]. It is not yet possible to estimate the importance *in vivo* of the inactivation of serotonin by a sulfotransferase system that has recently been detected in the brain[157, 158].

The monoamine oxidases (MAO), which are located in the mitochondria[118], are partly responsible for the regulation of the amine concentration in the cells. These are flavoproteins[159, 160] containing Cu^{2+}. Mitochondria preparations exhibit an MAO activity toward all monoamines. The activity of the monoamine oxidases de-

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creases in the order tyramine > dopamine > tryptamine > serotonin > norepinephrine; they have no stereospecificity[161,162].

Though the monoamine oxidases have been known for more than thirty years, it was only recently that their heterogeneity was detected directly. Four enzymes having different substrate specificities from brain and liver mitochondria were separated from one another electrophoretically[163–168]. The importance of these various monoamine oxidases to the catabolism of monoamines in the central nervous system cannot be decided until it is known whether different monoamine oxidases are located in different mitochondria or whether all mitochondria have the same enzyme pattern. A monoamine oxidase also catalyzes the oxidation of 1-methyl-4-histamine to 1-methylimidazolylacetic acid (cf. Scheme 4). The direct oxidation of histamine, which is effected in the peripheral organs by a diamine oxidase[169], probably does not occur in the brain, since the diamine oxidase activity in this organ is very low. The main path for the physiological inactivation of histamine is thus methylation on the imidazole nitrogen by the histamine *N*-methyltransferase[148]. Dimethylhistamine is observed only after administration of large quantities of histamine[170].

3.3. Storage and Liberation

A starting point for the intensive study of the biogenic amines in the brain, apart from their nonuniform distribution (cf. Table 1), was the observation that the concentrations of several amines in the brain are increased by monoamine oxidase inhibitors and reduced by reserpine and reserpine-like substances, the changes in the amine concentration in the brain being accompanied by pronounced changes in mood, affect, and behavior[171]. To gain an understanding of the chemical, biological, and pharmacological relationships, it was necessary first to localize the amines within the organism, in the individual organs, and finally in certain cells and cell elements.

Norepinephrine, dopamine, and serotonin were detected in the nerve cells of numerous regions of the brain and in the nerve fibers with their terminal arborizations, as well as in the endings of the sympathetic nervous system, by the histochemical fluorescence method (cf. Section 2.6). Evidence that the biogenic amines in the brain are located in specific neurons was also found[172–176]. It was also shown by electron-microscopic autoradiography that [^{3}H]-norepinephrine that had been injected into a ventricle of the brain was stored in the nerve cells and terminals[177].

Particularly significant clues to the functioning of the biogenic amines have been obtained from their localization within the synapses, the junctions between two nerve cells. Thus by centrifugation of the crude mitochondria fraction from brain homogenate in density gradients, it was possible to separate particulate fractions that could be identified by electron microscopy as the

Table 2. Distribution of the biogenic amines and some enzymes connected with their metabolism in the submitochondrial fractions from brain homogenate. (The numerical values in the table are relative concentrations or relative activities, *i. e.* the percentage of amine or enzyme activity found in the fraction in question divided by the percentage of protein found.)

Amine or enzyme	Myelin	Small nerve endings	Nerve endings I	Nerve endings II	Mitochondria	Ref.
Noradrenaline	0.32	2.05	1.66	0.77	0.72	[261]
Dopamine	0.79	1.85	1.13	0.91	0.71	[261]
Serotonin	0.61	0.78	2.17	0.76	0.48	[260]
Histamine	0.72	2.70	1.65	0.44	0.70	[181]
Acetylcholine	0.15	2.24	2.99	0.94	0.58	[262]
Tyrosine hydroxylase	2.28	2.43	1.83	0.54	0.36	[263]
Tryptophan hydroxylase	0.83		1.7		0.47	[264]
Dopa-decarboxylase	1.09	1.26	1.47	0.90	0.87	[263]
Monoamine oxidase	0.36	0.42	0.53	0.88	1.39	[263]
Na-K-ATPase	0.96	1.12	1.24	1.23	0.16	[263]
Acetylcholine esterase	1.51	1.26	1.35	0.94	0.77	[263]
Choline acetylase	1.72	1.95	1.46	0.86	0.79	[263]
Catecholamine *O*-methyltransferase	0.54	0.94	1.02	1.42	1.01	[180]

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Figure 2. Electron micrograph of synapses from the region of the substantia nigra of the rat. M = mitochondria; V = clear synaptic vesicles; DV = granulated synaptic vesicles (dense core vesicles); PrM = presynaptic membrane; PoM = postsynaptic membrane; G = gliacell; De = dendrite. (Photograph by Dr. *I. J. Bak*, Frankfurt/Main; magnification 40000×)

severed endings of the nerve cells[178,179]. As can be seen from Table 2, the amines and also the enzymes that are associated with the metabolism of the amines were found in these nerve endings, and it must therefore be concluded that the synapses are not only morphological but also biochemical units.

Figure 2 shows an electron micrograph of central synapses. Apart from the mitochondria, which are regularly found in the synaptic apparatus, and the thickened presynaptic and postsynaptic membranes, the numerous vesicles are particularly striking. In addition to clear, round vesicles having a diameter of 400–600 Å, granulated vesicles having a diameter of 800–1200 Å are observed. Smaller granulated vesicles are typical of peripheral sympathetic nerve endings.

De Robertis was able to detect directly the storage site of biogenic amines in vesicles by bursting the membranes of the severed nerve endings by an osmotic shock, separating the vesicles from the other membrane fractions by centrifugation in a density gradient[180–184], and demonstrating the presence of the biogenic amines in the vesicle fraction. It was also shown that radioactively labeled biogenic amines are taken up by the vesicles[185–190].

Uchizono[191] was the first to draw attention to clear oval vesicles having a diameter of 400–600 Å. These are regarded by this author as the vesicles of the inhibitory neurons, and are thought to contain γ-aminobutyric acid as the transmitter substance. However, it has not yet been possible to separate the vesicles of various types from one another, and it is by no means certain whether a synapse stores the same amine or various substances in its various kinds of vesicles.

The outstanding importance of the discovery of the amine-storing vesicles is evident in the light of the views developed concerning the manner in which the biogenic amines function as neurochemical transmitter substances, and particularly of *Katz*'s hypothesis[192], according to which the transmitter substances are liberated from the synaptic store not as single molecules but simultaneously in large numbers. The vesicles could be regarded as the morphological equivalent of this quantum hypothesis.

Synapses are also found on the surface of dendrites, on the cell bodies themselves, and on the axons. A potential of about −70 mV is normally maintained by the nerve cells between the interior of the cell and the external medium. If this membrane potential is reduced sufficiently at any point of the cell membrane by some suitable means, it collapses entirely. A pulse of electricity is formed and spreads out in all directions. The height of the pulse, the velocity with which it spreads out, and its time course are determined by the anatomical details of the nerve cell in question. The pulse passes through the axon to the synapses of other nerve cells. A distinction is made between excitatory and inhibitory neurons. The pulse coming from an excitatory neuron acts through the corresponding synapses to produce a partial depolarization of the neuronal membrane, and so facilitates the formation of an electric pulse; inhibitory neurons, on the other hand, cause hyperpolarization of the neuronal membrane. They thus inhibit the formation of a pulse. Since both excitatory and inhibitory synapses terminate on the nerve cells in large numbers (possibly as many as 50000), and since these can act simultaneously or successively in a certain time sequence on the nerve cell, very fine control can obviously be exerted on the nerve cells by this means.

Apart from *T. R. Elliott*'s classic discovery (1905) that the action of epinephrine is equivalent to that of a sympathetic impulse and the experiments by *O. Loewi* (1923), in which the liberation of acetylcholine in the heart of a frog on stimulation of the vagus nerve and the production of a nerve impulse by the liberated acetylcholine were detected, physiological arguments in particular have been responsible for the development of the view that the transmission of stimuli from one nerve cell to another at the synapse proceeds essentially by a chemical mechanism:

1. The synapse presents a high resistance to electric current in both directions.

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2. Whereas the axon can conduct an impulse in both directions, the conduction at the synapse is strictly unipolar, *i.e.* only those electric impulses that come from the presynaptic fiber are conducted.
3. The conduction of the impulse at the synapse is delayed by somewhat less than 1 ms. It may be assumed that this delay corresponds to the time required for the liberation of the transmitter substance and its transport to the receptor.

The transfer of stimuli is purely physical only in ephaptic junctions[*], which are rare in the animal kingdom.

The hypotheses developed at first were concerned mainly with the mode of transmission of stimuli at the synapses for acetylcholine as the transmitter substance, particularly on the basis of investigations of the muscle end plates and certain ganglia. These views were later applied to the action of norepinephrine and serotonin[193]. The most important of these views are shown schematically for norepinephrine in Figure 3.

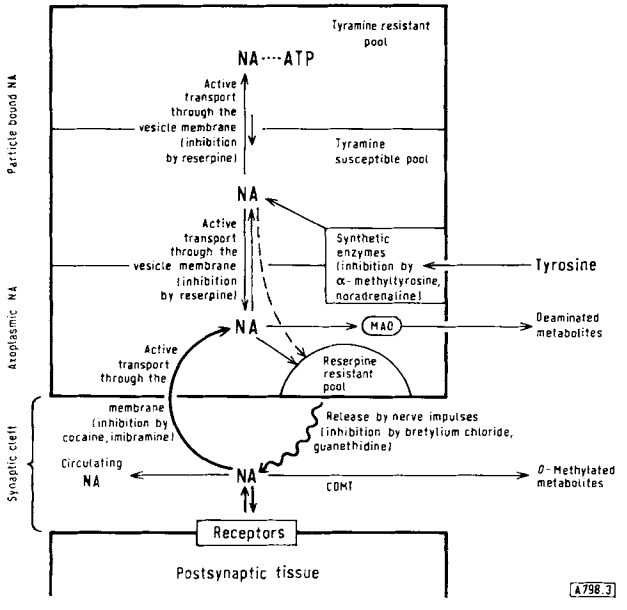


Figure 3. Scheme of the views on the mode of action of a noradrenergic synapse (based on [201]). NA = norepinephrine, MAO = monoamine oxidase, COMT = catecholamine *O*-methyltransferase, imipramine = *N*-(3-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine hydrochloride, bretylium chloride = ethyl-*o*-bromobenzyldi-methylammonium chloride, guanethidine = 2-(octahydro-1-azocinyl)ethylguanidinium sulfate.

From the synthesis of an amine molecule until it exerts its physiological action and is finally converted into a physiologically inactive derivative, its life cycle consists essentially of the following stages[194]:

1. Active transport of the amino acids (tyrosine, tryptophan, histidine) through the blood-brain barrier and through the neuronal cell membrane. This step is catalyzed by permeases.

2. Stepwise biosynthesis by hydroxylation and decarboxylation. The final step in the synthesis of norepinephrine, *i.e.* the β-hydroxylation of dopamine, takes place on the vesicle membrane[195,196]. It has recently also been shown that the amine-degrading enzyme monoamine oxidase, which is normally localized in the outer mitochondrial membrane, is probably also present in the norepinephrine-storing vesicles of the heart[197].

3. Uptake of the amine into a storage vesicle by active ATP- and Mg^{2+}-dependent transport and its association with binding substances in the vesicle[198–200]. In this form, the amine is physiologically inactive. It is in dynamic equilibrium with other storage forms, the morphological equivalent of which has not yet been ascertained.

4. Physiological liberation of the amine by a nerve impulse. In this active form, the amine can combine with the receptor protein or other specific proteins (*e.g.* monoamine oxidase).

5. Dissociation of the amine from the receptor protein and termination of the physiological action.

[^{3}H]-Norepinephrine injected into the blood stream is preferentially stored in the vesicles of the endings of the sympathetic nervous system. Two storage forms of [^{3}H]-norepinephrine have been distinguished in these endings by application of tyramine. One form is resistant to tyramine, and the norepinephrine in this form is complexed with ATP; the other form can be readily depleted by tyramine, and is in equilibrium with the norepinephrine in the extragranular fluid. The position of the equilibrium between the axoplasmatic norepinephrine and that bound to particles is determined by the uptake and liberation of the amine by the vesicles and its metabolic transformation by the monoamine oxidase.

An impulse arriving through the presynaptic nerve fiber presumably releases norepinephrine from a small pool, which cannot be emptied either by tyramine or by reserpine[201]. It diffuses from this store into the synaptic cleft and to the receptor. The combination of the amine with the receptor protein causes a specific change in the permeability of the neural membrane to ions, and hence in its polarization.

[*] Ephaptic or electronic junctions, like the synapses, are interphases provided for the transmission of stimuli, but have a relatively low electrical resistance. They occur mainly in the nervous systems of lower animals. They have not so far been observed in the central nervous systems of mammals.

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The action of the amine on the receptor is terminated *e.g.* in the case of norepinephrine by active re-uptake, which takes place in the axonal membrane. The amine passes very rapidly from the axoplasm into the storage granules. A small proportion of the norepinephrine liberated by the nerve impulse is inactivated by 3-*O*-methylation. This reaction is catalyzed by catecholamine *O*-methyltransferase.

Our views on the mode of action of an adrenergic synapse (*i.e.* a synapse in which norepinephrine appears to act as the chemical transmitter substance) agree with numerous pharmacological experiments, which cannot be discussed in detail here. They can also be applied to the mode of action of a central noradrenergic synapse, and probably also in principle to the mode of action of dopamine, serotonin, and histamine in special synapses, though experimental observations on these amines are few. Apart from a few differences, these views are also applicable to the mode of action of acetylcholine at a cholinergic ending[202]. Acetylcholine, like norepinephrine, is bound in granular form in stores that differ in the ease with which they can be emptied, and a small proportion is also present in the axoplasm. Unlike norepinephrine, however, the acetylcholine liberated by a nerve impulse and associated with the receptor is hydrolyzed into choline and acetic by the acetylcholine esterase bound in the postsynaptic membrane[118,179], and its physiological action is thus terminated. The active reuptake of the choline into the synapse formally corresponds to the transport system that is responsible for the termination of the action of norepinephrine.

Norepinephrine is thought to be the transmitter substance not only in the noradrenergic neurons of the central nervous system but also in the endings of the postganglionic fibers of the sympathetic nervous system, while acetylcholine is regarded as the transmitter substance of the preganglionic fibers of this system and of the parasympathetic nervous system. However, acetylcholine esterase[203] and acetylcholine[204] have now also been found in sympathetic ganglia. These and many other pieces of evidence[205], which were first gathered together by *Burn* and *Rand*[206,207], led to the development of an interesting hypothesis, which is partly placed in doubt by the above picture of the mode of action of norepinephrine.

This hypothesis says in essence that the acetylcholine initially liberated by the nerve impulse in a cholinergic synapse liberates a further quantity of acetylcholine in a second step, and that this further acetylcholine is responsible for the transmission of the stimulus. Similarly, primarily liberated acetylcholine would cause the liberation of norepinephrine in a noradrenergic synapse.

The processes that take place between the arrival of a nerve impulse and the liberation of the transmitter substance of a synapse are not yet known. Our knowledge about the chemical nature and the mode of action of the receptors is also still unsatisfactory. Initial studies indicate that the receptor molecules in the postsynaptic membrane may be proteolipids[208]. Speculations on the structure of the adrenergic receptors and the importance of adenyl cyclase as an adrenergic receptor will not be discussed here (cf.[209–213]).

3.4. Turnover

The turnover of an amine in the brain is a measure of the rate at which the entire pool present is replaced. The amine is supplied to the pool by synthesis, and leaves it by metabolic transformation and to a small extent with the blood stream. It is uncertain, however, what proportion of the amine disappears from the pool because of metabolic transformation within the neuron and what proportion has been liberated by the neuronal activity and then transformed metabolically. Thus a high turnover rate cannot be equated directly to a high physiological activity.

The turnover rates of the amines in the brain can in principle be determined as follows: measurement of the decrease in the amine metabolite concentration after inhibition of the degradation of the amine, *e.g.* by monoamine oxidase inhibitors[214]; measurement of the rate of accumulation of the amine metabolites after inhibition of their transport out of the brain, *e.g.* by probenecid (*p*-dipropylsulfamoylbenzoic acid)[214–216]; determination of the decrease in the amine concentration after inhibition of the rate-determining step of the synthesis, *e.g.* by inhibition of the hydroxylation of tyrosine by α-methyl-*p*-tyrosine[217,218]; measurement of the rate of accumulation of radioactivity in the amine pool after constant perfusion (or after a single injection[219,220]) with the substrate of the rate-determining step of the amine synthesis. If it is assumed that injected amine can enter freely into equilibrium with the endogenous pool, the turnover rate can also be determined by measurement of the decrease in the radioactivity of the amine pool after equilibration of the pool with exogenous radioactive amine[220].

The measurements have shown surprisingly long half-life times for the biogenic amines in the various regions of the brain. Thus a half-life time of two hours was found

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for norepinephrine with a turnover of 58 $ng.g^{-1}h^{-1}$ in the cerebellum and 4 h with a turnover of 328 $ng.g^{-1}h^{-1}$ in the hypothalamus[221]. It must be understood that the turnover measurements, in addition to their shortcomings, reflect only the turnover of a large population of neurons. The measurements do not provide an insight into the different turnover rates of small active amine pools, in which it is now thought that the amine synthesis proceeds, and which are also preferentially involved in the transmission of stimuli at the synapses, but which undergo only a slow exchange with the amine stored in the other pools. Nevertheless, turnover measurements give important indications of changes in the physiological state of the nervous system[217]. Thus by electric stimulation of the sympathetic nervous system, the rate of the norepinephrine synthesis can be increased by a factor of 5 to 6 with no increase in the amine concentration[225]. The absorption of exogenous norepinephrine in the endings of the sympathetic nervous system is in fact reduced under these conditions[226].

According to observations made so far, serotonin and dopamine have higher turnover rates in the central nervous system than norepinephrine[143,214].

The amine-storing vesicles, which are presumably formed in the cell body and transported along the axon to the endings at a speed of 0.5–10 mm/h, have a very much longer half-life time than the amine pool, *i.e.* 5–10 weeks[222–224].

4. Biogenic Amines and Behavior

4.1. Temperature Regulation and Biological Rhythms

The strong influence of the environmental temperature on the turnover rate of norepinephrine and serotonin in the brain and on the concentration of these amines[220,227] led to hypotheses regarding the importance of the biogenic amines to the regulation of the body temperature, particularly since the greatest changes in the turnover rates were observed in the hypothalamus, which has been regarded, since the classic investigations by *Magoun* and *Ranson,* as the site of the temperature regulation center. Another argument favoring the participation of the amines in the temperature regulation was provided by the observation that injections of norepinephrine and serotonin into the third ventricle of the cerebrum, *i.e.* into the neighbourhood of the hypothalamus, lead to changes in the body temperature[227–230].

Nearly all rhythms in mammals are controlled by internal biological clocks, with whose operation the biogenic amines frequently appear to be connected. Most of these rhythms with a period of about 24 hours are matched to the daily cycle of light and darkness, but they are retained even when the animals are deprived of the ability to perceive the change in light. These rhythms are described as circadian. An example of such a rhythm is the waking and sleeping rhythm. This is accompanied by a pronounced change in the serotonin concentration in the brain, while the norepinephrine concentration changes only slightly[231,232]. Recent electrophysiological and pharmacological studies have provided important insights into the importance of serotonin and norepinephrine to the sleeping and waking cycle[233]. The most important discovery was the fact that inhibition of the serotonin synthesis by *p*-chlorophenylalanine at the tryptophan hydroxylation stage causes insomnia, which can be eliminated by injection of 5-hydroxytryptophan. Insomnia has also been produced by total destruction of the serotoninergic neurons in the raphe system (an extensive network of fibers in the brain stem, cf. Fig. 1). Monoamine oxidase inhibitors cause complete suppression of paradoxical sleep and prolong synchronized sleep (slow wave sleep).

According to recent physiological results, sleep comprises these two forms, which can be very clearly distinguished and quantitatively determined by the difference in the electrical activity of the brain, in the tone of the neck musculature, and in the frequency of eye movements. It should be noted that dreaming occurs only during paradoxical sleep.

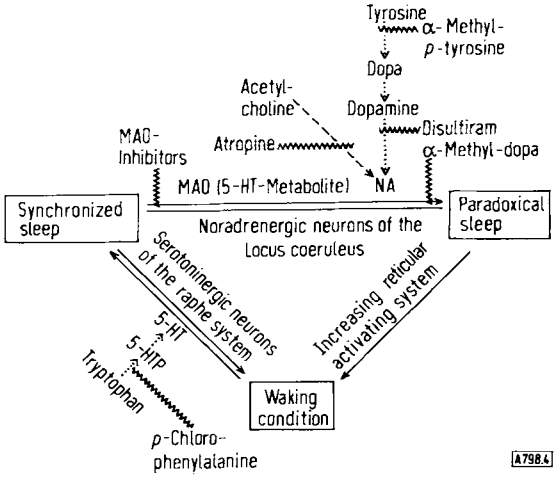


Figure 4. Scheme illustrating the relationships of the forms of sleep and of the waking state to one another and the serotoninergic and noradrenergic mechanisms that could be involved in the sleeping-waking rhythm (based on [233]). NA = norepinephrine, MAO = monoamine oxidase, 5-HT = serotonin (5-hydroxytryptamine), 5-HTP = 5-hydroxytryptophan, disulfiram = tetraethylthiuram disulfide.

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Figure 4 shows a scheme of possible relationships between the forms of sleep and the aminergic mechanisms that control them. The transition from the waking state to synchronized sleep is the responsibility of groups of neurons that are controlled by synapses with serotonin as the transmitter substance. The next step in the cycle requires both certain serotonin metabolites, whose formation can be suppressed by monoamine oxidase inhibitors, and norepinephrine for the initiation process. The corresponding nerve cells have been located in the locus coeruleus (cf. Fig. 1). The norepinephrine-initiated processes that are necessary for the transition from synchronized sleep to paradoxical sleep can be inhibited at several points in the norepinephrine metabolism as well as by "false transmitter substances" (*e.g.* α-methyldopa). Atropine also prevents the final step to paradoxical sleep, presumably by inhibiting an acetylcholine-dependent trigger mechanism.

A striking rhythmic variation of the concentration of the biogenic amines in the pineal body is directly controlled by the action of light on the retina. The pineal body appears in turn to be functionally linked with rhythmic endocrine variations (*e.g.* the menstrual cycle)[234]. A rhythmic variation of the catecholamine concentration that parallels the menstrual cycle has also been observed in the nerve cells of the hypothalamus[235].

4.2. Ontogenetic and Pharmacological Aspects

In view of the idea that the biogenic amines function as neurochemical transmitter substances, one should expect normal amine concentrations in the brain to be fundamentally necessary for normal brain function and hence for normal behavior. This statement must not be taken to mean that certain average concentrations of the amines in the brain could be explained by certain types of behavior or moods. This type of thinking would be inadmissible in connection with such a highly differentiated organ as the brain. Nevertheless it frequently has to be used as a first step along the road to an understanding of the complex relationships, since the individual functional units cannot always be analyzed *per se*, for experimental reasons.

Newborn guinea pigs (which are nidifugous animals) have substantially the same amine contents in the brain as the adult animals, and their behavior is accordingly comparable with the adult behavior. On the other hand, rats, which are nidicolous, have lower percentage amine contents in the brain at birth than as adult animals. These low contents correspond to their immature behavior patterns[118,236–238]. However, these observations are by no means general for all nidifugous and all nidicolous animals (cf.[239]).

As was mentioned earlier, very pronounced changes in behavior are produced by certain drugs that can alter the concentration of the biogenic amines by interfering with their metabolism. The best-known example is the strongly sedative action of reserpine and related substances, which cause a decrease in the norepinephrine, dopamine, and serotonin concentration in the brain. The sedative action of these substances can be cancelled by injection of dopa, the precursor of the catecholamines, but not by injection of 5-hydroxytryptophan, the precursor of serotonin[240,241]. These observations show that the sedation is associated with the decrease in the catecholamine concentration, but not with the decrease in the serotonin level[242]. With the decrease in the amine concentration, the granulated vesicles (dense core vesicles) disappear from the central noradrenergic synapses[194,243,244] and from the endings of the sympathetic nervous system[245]. The action of reserpine appears to result from inhibition of the uptake of the amines into the vesicles (by blockage of the ATP- and Mg^{2+}-dependent transport). Substances that selectively inhibit the biosynthesis of the catecholamines, such as α-methyltyrosine, like reserpine, cause sedation and related behavioral changes[224].

The strongly tranquilizing action of chlorpromazine and related phenothiazines, however, is not due to a decrease in the norepinephrine concentration. Among its very numerous biochemical effects, that which best explains this action is probably the decrease in the permeability of some cellular and subcellular membranes to amines[173]. The hypothermia observed on treatment with chlorpromazine is probably also a result of the reduced response of the receptors in the hypothalamus to norepinephrine[194]. Chlorpromazine also blocks the dopaminergic receptors[224].

It was recognized a few years ago that the serotonin concentration in the brain can be selectively reduced with the aid of *p*-chlorophenylalanine. This compound acts *in vivo* as an irreversible inhibitor of the hydroxylation of tryptophan[246]. A decrease in the serotonin concentration to 10% of the normal value surprisingly causes only very small changes in the overall behavior, apart from an increase in irritability[194], so that very little can be said at present about the importance of the serotonin concentration to behavior. It must be assumed that the remaining 10% of the serotonin is sufficient to fulfil its function as a transmitter substance for the serotoninergic neurons, just as the small quantity of catecholamines that are stored in a reserpine-resistant form is sufficient to maintain the transmitter function[194].

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The concentration of the biogenic amines in the brain cannot be increased by injection of the amines into the blood stream, since they cannot pass through the blood-brain barrier. Their concentration can however be significantly increased by injection of their precursors (amino acids) and by inhibition of the catabolic reactions of the amine metabolism. Monoamine oxidase inhibitors have been in use for a long time in the treatment of depressions, since the increase in the amine concentration in the brain after inhibition of the monoamine oxidase is followed by an increase in activity and drive. After a 50% inhibition of the enzyme, the serotonin concentration in the brain of the rat increases by about 100%. Dopamine generally behaves very similarly to serotonin, whereas the concentration of norepinephrine increases very much less. The reason for this is its increased 3-*O*-methylation[173].

It cannot be concluded directly that the increase in drive and the antidepressant action following the inhibition of the monoamine oxidase is due to the increased dopamine or serotonin content, since the concentration of tyramine and possibly of many other amines that have not yet been considered, but which could be responsible for the changes in behavior just as are dopamine, serotonin, norepinephrine, or histamine, is also increased. It should be pointed out here that many amines such as bufotenine, dimethyltryptamine, mescaline, and amphetamine that are structurally very close to serotonin or the catecholamines have a strongly excitatory or hallucinogenic action even in very small concentrations.

The increased motor activity and the antidepressant action of imipramine and related substances are not due to an increase in the total amine concentration. On the contrary, imipramine inhibits the active re-uptake of norepinephrine and serotonin in the synapses (cf. Fig. 3), and so prolongs the action of these substances on the receptor. Desipramine has a similar effect on noradrenergic neurons, but does not inhibit the neuronal serotonin pump. The imipramine group as a whole appears to have no action on dopaminergic neurons[224].

Even these few examples show that a similar gross behavior can result from very different molecular processes. As was indicated earlier, the action of biogenic amines on the behavior is due to the fact that monoaminergic neurons innervate practically all parts of the central nervous system, and are therefore involved in the central regulation of autonomic, motor, and endocrine functions, as well as of integrative mechanisms such as conditioned avoidance response, mood, and drive. The aminergic neuron systems can act more or less as a unit *e.g.* by modification of the excitability of large parts of the brain. However, each aminergic neuron system can also respond separately to certain stimuli, particularly under the action of certain drugs that have different effects on the various types of receptors[224].

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5. Neurological and Psychiatric Disturbances

An excellent example of the effect of the absence of a certain monoaminergic neuron system is the Parkinson syndrome. From the standpoint of pathological anatomy, this disease is characterized by the loss of cells in certain parts of the extrapyramidal motor system, particularly in the substantia nigra[247]. The strikingly low dopamine content in structures of the corpus striatum (nucleus caudatus, putamen, globus pallidus) of sufferers from Parkinson's disease[143] and many other observations indicate the importance of this amine to the occurrence of the abnormal movements of the patients. This assumption was confirmed by the action of L-3,4-dihydroxyphenylalanine, which leads to the disappearance of the serious clinical symptoms of parkinsonism, *i.e.* akinesia and rigor. On the basis of electrophysiological and pharmacological studies, it is assumed that the cholinergic fibers leading to the corpus striatum (striopetal system) activate the striatal cells, whereas a dopaminergic system has an inhibiting action on these cells. Because of the dopamine deficiency in the corpus striatum of parkinsonian patients, the cholinergic system becomes unbalanced and initiates the motor disturbances *via* descending fibers[248, 249]. The causes of the dopamine deficiency in the striatal system of parkinsonian patients have not yet been fully elucidated.

The influence of changes in the amine concentrations in the brain on mood and drive, as well as the knowledge of substances that can produce states very similar to those observed in endogenous psychoses, led at a very early stage to speculations on the role of the biogenic amines in the causality of these mental deteriorations, manic-depressive psychoses, and schizophrenias.

The catecholamine hypothesis (*J. Harley-Mason, J. R. Smythies,* and *H. Osmond,* 1952) is based on the close structural relationship of norepinephrine, dopamine, and mescaline (β-3,4,5-trimethoxyphenylethylamine), an effective hallucinogen. This led to the assumption that abnormal methylation products of norepinephrine or of dopamine with psychotoxic properties could be formed in the schizophrenic organism.

The pharmacological antagonism between serotonin and LSD-25 (D-lysergic acid diethylamide) led to the assumption that the serotonin metabolism could be abnormal in schizophrenia (*J. Gaddum* and *D. W. Woolley,* 1954; serotonin hypothesis). The discovery of the hallucinogenic action of *N*-methylated tryptamines led *Szara* to apply the hypothesis of abnormal methylation products to tryptamine derivatives (tryptamine hypothesis). The fourth hypothesis, which was proposed by *S. S. Kety et al.,* is closely related to the others. Following from plausible assumptions based on observations of the action of tryptophan and methionine on the behavior of schizophrenics, it is assumed that the schizophrenic organism carries out abnormal transmethylations (transmethylation hypothesis).

These hypotheses stimulated very many investigations on the amine metabolism in healthy and diseased organisms. It would be beyond the scope of this review to fol-

low even only the most important of these investigations in broad outline (cf. *e.g.*[250]). Neither a biochemical cause nor a biochemical correlate of endogenous psychoses has so far been found[251], though the relation between disease and amine metabolism appears to be obvious in the case of the endogenous depressions. Thus the symptoms of the depression are modified by measures that affect the amine metabolism in the brain. Monoamine oxidase inhibitors and substances of the imipramine type have an antidepressant action, while treatment with lithium chloride leads to an improvement of the symptoms[252] and causes an increase in the turnover of norepinephrine in the brains of experimental animals as well as increased metabolic transformation of this amine by the monoamine oxidase[253–255]. Depressions that are frequently indistinguishable from endogenous depressions can be produced again by treatment with reserpine[256]. There are also numerous observations that point to differences in the amine metabolism of diseased persons as compared with healthy subjects, but no conclusions can be drawn as yet from these observations on critical examination[257].

There are many reasons why our knowledge about the biochemistry of mental diseases is still very limited despite great efforts, quite apart from whether the approach *via* the amine metabolism, which is only one of the many possible approaches to the understanding of these diseases, does in fact lead to the desired result. One of the most important reasons seems to us to be as follows. To be able to recognize pathological modes of reaction, it is necessary to know the physiological processes for comparison. However, the biochemistry of the central nervous system is still largely unknown, even in a field that has been studied as intensively as that of the biogenic amines.

6. Closing Remarks

The function of some biogenic amines as transmitter substances at certain synapses can now be regarded as certain, though their precise mode of action is not yet known and very many questions remain to be answered in connection with the functioning of the synapses. The undeniably significant expansion of our knowledge concerning the biogenic amines during the past few years is an excellent example of the fact that progress in biology can only be achieved by the combined efforts of workers in a wide range of disciplines, *i.e.* biologists, morphologists, physiologists, pharmacologists, and chemists.

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COMMUNICATIONS

Oxidative Addition of Nitroalkanes to Tetrakis(triphenylphosphane)platinum(0): a Simple Route to Complex Metal Fulminates

By *Wolfgang Beck, Karl Schorpp,* and *Franz Kern*[*]

Dedicated to Professor Walter Hieber on the occasion of his 75th birthday

Complex metal fulminates have hitherto been synthesized by treatment of alkali-metal fulminates [accessible from $Hg(CNO)_2$ and the alkali-metal amalgam] with metal salts[1,2]. Although fulminatometalate anions with bulky cations, and complexes containing phosphanes, are not explosive and are relatively stable[2], work with the starting materials [NaCNO and $Hg(CNO)_2$] requires particular care.

We have now found that reaction of tetrakis(triphenylphosphane)platinum(0) with nitromethane provides a convenient and completely safe method of preparing difulminatobis(triphenylphosphane)platinum(II)[3].

$$Pt(PPh_3)_4 \rightleftharpoons Pt(PPh_3)_2 + 2\ PPh_3$$

$$Pt(PPh_3)_2 \xrightarrow[C_6H_6/C_2H_5OH/H_2O]{CH_3NO_2/80\,^\circ C} \left[\begin{array}{c} Ph_3P \quad CH_2 \\ H\text{-}Pt \quad N \\ Ph_3P \quad O \quad O \end{array}\right]$$

$$\xrightarrow[2.\ -\,2\ H_2O;\ -\,H_2]{1.\ +\ CH_3NO_2} O\text{-}N{\equiv}C\text{-}\underset{\displaystyle PPh_3}{\overset{\displaystyle PPh_3}{Pt}}\text{-}C{\equiv}N\text{-}O$$

We assume that nitromethane reacts as a compound containing an acidic CH group in this process, primarily by oxidative addition, analogously to the reaction of $Pt(PPh_3)_4$ with other protonic acids[4]. Accordingly, the reaction medium is decisive for formation of fulminate: whereas no fulminate can be detected

after 70 hours' heating under reflux in benzene/nitromethane, the fulminato complex is formed in 80% yield in ethanol/-water/benzene/nitromethane (1:1:1:3)[7] [cf. the acidity of nitromethane: pK (in H_2O) = 10.2[5]; pK (in an aprotic medium) = 15.96[6]].

If a large excess of triphenylphosphane is used, the cyano complex is the main product, fulminate being reduced to cyanide by the phosphane as in the reaction of organic nitrile oxides[8].

Reactions of $Pt(PPh_3)_4$ with nitroethane or 2-nitropropane do not lead to fulminates with loss of methanol or dimethyl ether, respectively, but instead the dinitro complexes $(PPh_3)_2Pt(NO_2)_2$ can be isolated.

Difulminatobis(triphenylphosphane)platinum(II)

$Pt(PPh_3)_4$ (1.25 g, 1 mmole) is heated under reflux in benzene/ethanol/water/nitromethane (1 : 1 : 1 : 3) (60 ml) under N_2 and with exclusion of light. Above 60 °C the solvent mixture forms one phase in which the platinum(0) complex dissolves completely within a few hours. After 50 hours the fulminato complex is partly precipitated even in the hot; it is filtered from the cooled reaction mixture and recrystallized from chloroform/light petroleum, forming colorless crystals that contain 1 mole of chloroform per formula unit of the complex (yield 0.75 g, 80%). IR: $2\nu_s(CNO)$ = 2325 cm^{-1}, $\nu_{as}(CNO)$ = 2190 cm^{-1}, $\nu_s(CNO)$ = 1153 cm^{-1}[3].

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Sensitized Chemiluminescence on Thermolysis of Phthaloyl Peroxide in the Presence of 9,10-Diphenylanthracene

By *Karl-Dietrich Gundermann, Manfred Steinfatt*, and *Helmut Fiege*[*]

As was recently described[1], weak chemiluminescence occurs when potassium *tert*-butoxide reacts with phthaloyl peroxide in dimethyl sulfoxide in the presence of fluorescein. We have now found that warming phthaloyl peroxide (1.5×10^{-2} mole/l) with 9,10-diphenylanthracene (10^{-5} – 10^{-3} mole/l) in dimethyl or diethyl phthalate for *ca.* 10 min at 50–70 °C causes a relatively strong blue chemiluminescence (λ_{max} = 435 nm) which reaches *ca.* 5% of the maximal intensity and 6–7% of the quantum yield of luminol emitting in the same spectral region.

The emission spectrum is identical with the fluorescence spectrum of 9,10-diphenylanthracene; this is thus a case of sensitized chemiluminescence due to transfer to the diphenylanthracene of the excitation energy liberated on decomposition of the phthaloyl peroxide. The latter is partly converted by the reaction into yellow, non-fluorescing products. When the concentration of diphenylanthracene used is less than that given above, the chemiluminescence ceases prematurely, but it can be restarted by addition of further diphenylanthracene. Investigation of the obviously complex mixture of products is in progress (for thermolysis of phthaloyl peroxide in benzene see[2]).

We did not find any chemiluminescence from these two components in other organic solvents. The luminescence is appreciably catalyzed by addition of a little water to the phthalic esters: it then begins already at 25 ° C, although it reaches only about 1/3 of the intensity, but the same quantum yield is obtained in 20 min as in the reaction without water. Glacial acetic acid has a strong quenching action. Oxygen[2] was not found to be inhibitory, but it does not appreciably increase the light emission.

Dibenzoyl peroxide affords no chemiluminescence under the above conditions.

Hercules et al.[3] recently studied the role of energy transfer processes in the chemiluminescence of compounds such as 3,6-diphenyl-1,2,4,5-tetroxane (dibenzylidene diperoxide), also in the presence of diphenylanthracene. The sensitized chemiluminescence occurring in that reaction is ascribed to triplet benzaldehyde and/or singlet oxygen as primary excited particles (species which do not come into consideration for phthaloyl peroxide) and is weaker by several orders of magnitude than that now reported for the first time.

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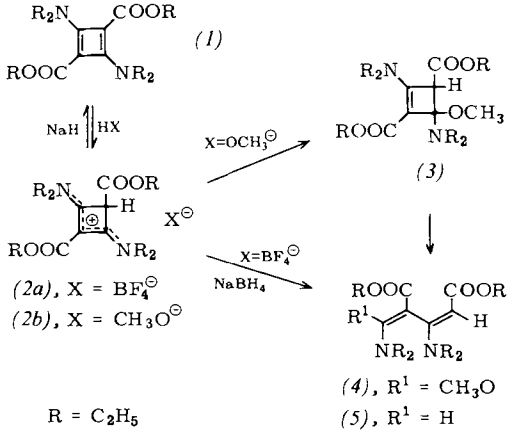
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Addition of Electrophiles to Diethyl 2,4-Bis(diethylamino)cyclobutadiene-1,3-dicarboxylate[**]

By *Rudolf Gompper* and *Günter Seybold*[*]

Owing to the known stability of cyclobutenecyanine salts, the "push-pull" substituted cyclobutadiene *(1)*[1] should be a strong nucleophile and thus make possible a study of the hitherto unknown reactions of electrophiles with cyclobutadienes.

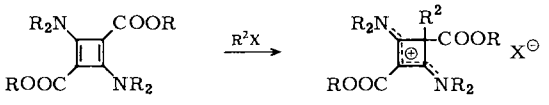
On reaction with strong acids such as HBF_4 in ether, compound *(1)* is converted quantitatively into protonated products, *e.g.* *(2a)*, from which it may be regenerated by treatment with sodium hydride[1].



Weak acids such as methanol add momentarily to *(1)*: initially formed cyclobutenecyanine cation immediately combines with methoxide ion to give cyclobutane derivative *(3)*, which escapes isolation by rearrangement to the stable butadiene derivative *(4)* [colorless oil, $n_D^{23} = 1.5282$][2]. The proposed structure *(4)* is based on the ^{1}H-NMR spectrum [in $DCCl_3$: $\tau = 5.25$ (1H/S); $\tau = 5.9$ and 6.6 (15H/M); $\tau = 8.8$ (18H/M)] and the IR spectrum [1680, 1550 cm^{-1}]; according to ^{1}H-NMR *(4)* is probably present as a mixture of geometric isomers. The finding that *(2a)* quantitatively yields the butadiene *(4)* on treatment with sodium methoxide in methanol supports the intermediacy of *(2b)*.

Compound *(2a)* reacts with $NaBH_4$ in acetonitrile at room temperature to give the butadiene *(5)* [colorless crystals, m.p. 53–55 °C] whose structure is confirmed by the ^{1}H-NMR spectrum [in $DCCl_3$; $\tau = 2.5$ (1H(-CH=)/S); $\tau = 5.25$ (1H(-CO-CH=)/S); $\tau = 5.9$ (4H(O-CH_2)/split Q); $\tau = 6.75$ (8H(N-CH_2)/M); $\tau = 8.8$ (18H (CH_3)/M)] and the IR spectrum [1700, 1605, 1560 cm^{-1}][3].

Compound *(1)* adds bromine very rapidly to form the 1:1 adduct *(6a)*, which crystallizes very poorly. On replacement of bromide ion by perchlorate ion (silver perchlorate in water/ethanol), a perchlorate is obtained that crystallizes very well [colorless needles, m.p. 111 °C] and whose IR spectrum [vCO = 1750, 1700, vC=C = 1605 cm^{-1}], UV spectrum [in $HCCl_3$; $\lambda_{max} = 289$ nm, log $\varepsilon = 4.49$], and ^{1}H-NMR spectrum (see Table) are compatible only with structure *(6b)*.



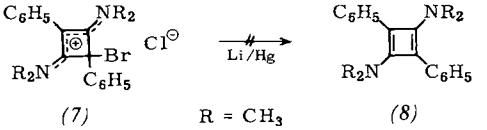
(1) R = C_2H_5 — *(6a), (6b), (9)-(11)*

Cpd.	R^2	X	^{1}H-NMR [b] OCH_2 (8H)	NCH_2 (8H)	CH_3 (18H)	R^2
(6a)	Br	Br				
(6b)	Br	ClO_4	5.32 (Q) [a]	5.96, 5.28 (Q)	8.68 (M)	
(9)	$COCH_3$	ClO_4	5.6, 5.7 (Q)	5.95, 6.40 (Q)	8.65 (M)	7.45 (3H/S)
(10)	CH_3	I	5.6, 5.7 (Q)	6.2 (Q) [a]	8.6 (T)	8.1 (3H/S)
(11)	2,4,6-Cycloheptatrien-1-yl	ClO_4	5.6 (Q) [a]	6.1, 6.5 (Q)	8.7 (M)	3.5 (4H) 4.85 (2H/T) 7.15 (1H/T)

[a] Split.
[b] TMS as internal standard, τ values in ppm, $DCCl_3$ as solvent.

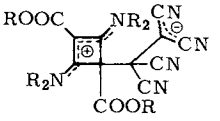
(6a) loses bromine very readily, even on heating in a melting-point tube. Its mass spectrum[4] corresponds to that of the cyclobutadiene *(1)*.

Reaction of *(6b)* with sodium hydride in toluene at about 70 ° C yields a yellow solution in which *(1)* can be detected by the diphenylcyclopropenone test[5]. Cyclobutadiene *(1)* is liberated from *(6b)* by treatment with lithium amalgam in toluene; *(1)* can then be intercepted by dimethyl acetylenedicarboxylate[6]. Attempts to remove halogen from *(7)*[7] under similar conditions and to detect the cyclobutadiene *(8)* have so far been unsuccessful.



(7) R = CH_3 *(8)*

Compound *(1)* adds equivalent amounts of acetyl bromide at temperatures as low as −40 ° C to give a colorless oil that crystallized after replacement of Br^- by ClO_4^-. The properties of the salt *(9)* [m.p. 71–72 ° C; IR spectrum (1740, 1720, 1595, 1090 cm^{-1}); ^{1}H-NMR spectrum, see Table] are in agreement with the proposed cyclobutenecyanine structure *(9)*. Analogous compounds are formed from *(1)* and methyl iodide [*(10)*, m.p. 110–112; IR spectrum (1738, 1698, 1603 cm^{-1}); ^{1}H-NMR spectrum, see Table] and tropylium perchlorate [*(11)*, m.p. 125–126 °C; IR spectrum (1735, 1710, 1585, 1090 cm^{-1}); ^{1}H-NMR spectrum, see Table].



(12)

Tetracyanoethylene and *(1)*, dissolved in toluene at −80 ° C, furnish a deep violet solution whose color is probably attributable to a charge-transfer complex. At −40 °C an almost colorless precipitate is formed which – when rapidly filtered off with suction – is stable for a few days at room temperature [colorless needles, m.p. 97–107 ° C (decomp.)]. In solution, however, rapid decomposition occurs with yellow coloration. Elemental analysis, ^{1}H-NMR spectrum [in SO_2 at −40 ° C: $\tau =$ 5.6 (4H(O-CH_2)/Q split); $\tau = 6.2$ and 6.5 (8H(N-CH_2)/Q); $\tau = 8.7$ (18H)/M], and particularly the IR spectrum [in $HCCl_3$; vCN = 2175, 2130, vCO = 1740, 1715, vC=C = 1585 cm^{-1}] establish the dipolar structure *(12)* of the reaction product. In contrast to the dipolar intermediate obtained from *(1)* and *p*-nitrobenzylidenemalodinitrile[6], no reaction products of definite composition could be isolated after the decomposition of *(12)* in methylene chloride. Isolation of the dipole *(12)* warrants particular attention in view of the reaction[8] of 1,2-diphenylcyclobutadiene with tetracyanoethylene.

General procedure:

A solution of the electrophile in a small volume of toluene is added to a solution of *(1)*, prepared in accordance with ref.[1], at low temperature in a Schlenk tube. After completion of the reaction the product is filtered off or isolated by evaporating the solution. Yields are almost quantitative in all cases.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *R. Gompper* and *G. Seybold*, Angew. Chem. *80*, 804 (1968); Angew. Chem. internat. Edit. *7*, 824 (1968).

[2] Butadiene was also isolated by *M. Neuenschwander* and *A. Niederhauser*, who have studied the addition of H_2O, NHR_2, and HOC_2H_5 to dimethyl 2,4-bis(dimethylamino)cyclobutadiene-1,3-dicarboxylate independently of us (*M. Neuenschwander*, personal communication; *M. Neuenschwander* and *A. Niederhauser*, Helv. Chim. Acta *53*, 519 (1970)).

[3] Cf. *T. Sasaki* and *A. Kojima*, Tetrahedron Lett. *1969*, 3639.

[4] Kindly recorded at Farbenfabriken Bayer AG, Leverkusen.

[5] *G. Seybold*, Dissertation, Universität München.

[6] *R. Gompper* and *G. Seybold*, Angew. Chem. *83*, 45 (1971); Angew. Chem. internat. Edit. *10*, 68 (1971).

[7] We are grateful to Professor *Viehe* for kindly supplying a sample of compound *(7)*.

[8] *P. Reeves, J. Henry*, and *R. Pettit*, J. Amer. Chem. Soc. *91*, 5888 (1969).

Cycloaddition to Diethyl 2,4-Bis(diethylamino)-cyclobutadiene-1,3-dicarboxylate[**]

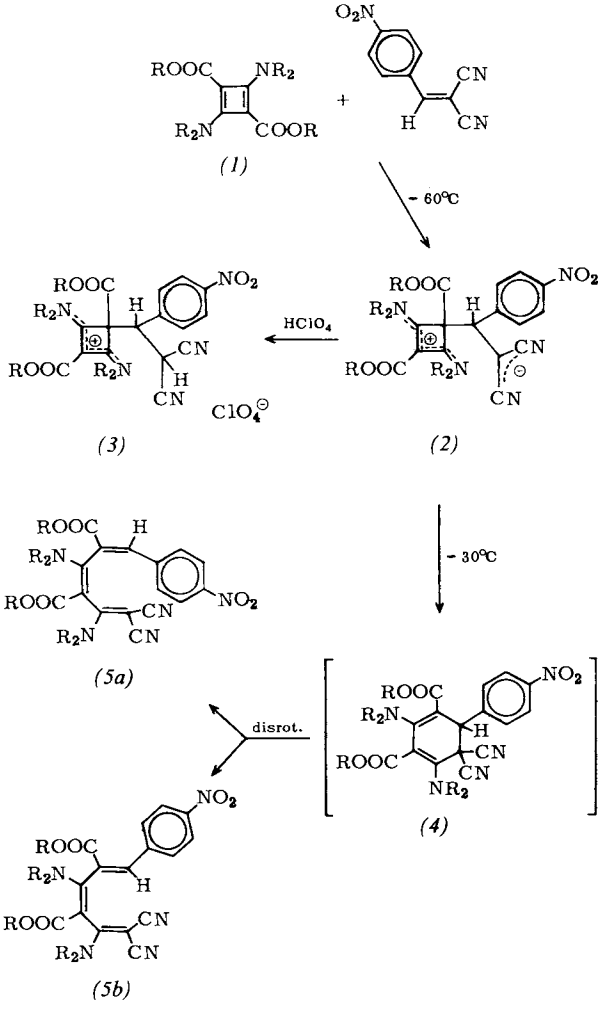
By *Rudolf Gompper* and *Günther Seybold*[*]

Cyclobutadiene is characterized by the pronounced readiness with which it undergoes cycloaddition with acetylenes, olefins, and other multiple bond systems. On stabilization by complex

formation with transition metals it completely loses this property. It was therefore of interest to establish whether, and if so to what extent, the "push-pull" stabilization in *(1)* affects the ability of this cyclobutadiene, which is stable at room temperature[1], to undergo cycloadditions.

Whereas *(1)* is inert towards the reactive but nonpolar CC double bond of norbornene, it reacts surprisingly well with electrophilic cycloaddends, even at low temperatures. The rapid reaction of *(1)* with simple electrophiles (HX, Br_2, CH_3I, CH_3COBr, and tropylium perchlorate)[2] and the stability of the resulting cyclobutenecyanine salts suggested the intermediacy of dipoles in cycloadditions to *(1)* in cases where the negative charge is sufficiently stabilized.

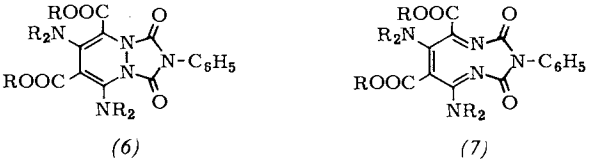
In fact, *p*-nitrobenzylidenemalodinitrile, which has already proved effective in forming dipoles in reactions with enamines[3] and ketene *S,N*-acetals[4], is found to react with *(1)* at −60° C to form a deep red solution from which an orange-yellow crystalline product can be precipitated with ether, whose properties, especially its low solubility in nonpolar solvents and its ease of protonation, indicate the dipole structure *(2)*. Protonation of *(2)* with anhydrous perchloric acid gives a quantitative yield of the colorless stable perchlorate *(3)* [correct elemental analysis; IR spectrum: νCO 1735, 1725, νC=C 1590 cm^{-1}].



R = C_2H_5

If a suspension of *(2)* in ether is warmed to −30° C, a yellow solution is obtained which yields an orange-yellow precipitate at room temperature. Repeated column chromatography of the precipitate furnishes two isomeric 1 : 1 adducts [of *(1)* and *p*-nitrobenzylidenemalodinitrile]; their IR spectra differ only slightly. A detailed study of the spectra shows (NMR) that the chemical shift of a signal due to a single proton at τ = 2.3 (in $DCCl_3$) and (IR) the stretching frequency of the cyano group at 2198 cm^{-1} and of the CC double bond at 1530 cm^{-1} are compatible only with the hexatriene structures *(5a)* and *(5b)*. Precise assignment of the isomers is not possible on the basis of the spectra alone. When the reaction mixture is warmed very slowly (3–4 h from −30° C to room temperature) the thermodynamically apparently more stable isomer is formed (yellow crystals, m.p. 144–146° C). In contrast, rapid warming gives mainly the less stable isomer (orange-yellow needles, m.p. 120° C) which quantitatively yields the yellow isomer on prolonged heating.

4-Phenyl-1,2,4-triazoline-3,5-dione combines with *(1)* at −80° C to give a crystalline, colorless 1 : 1 adduct [*(6)* or *(7)*].



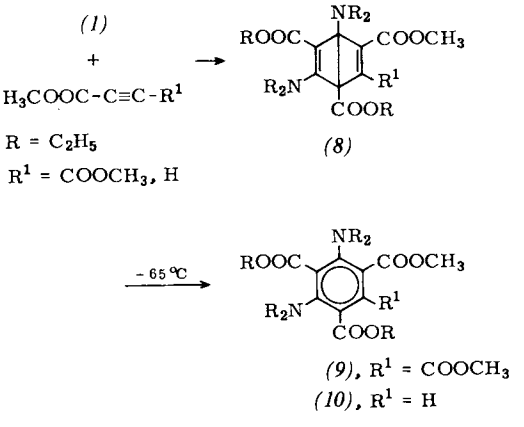
(6) *(7)*

R = C_2H_5

(7) would be expected to absorb in the visible region. Since the adduct is colorless (λ_{max} = 282 nm), we assign to it structure *(6)*. Attempts to convert *(6)* into *(7)* by heating were unsuccessful.

(1) also adds *N*-phenylmaleimide to give a 1 : 1 adduct (lemon-yellow needles, m.p. 140° C) whose structure probably corresponds to that of *(6)*.

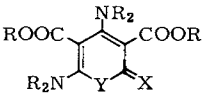
Reaction of *(1)* with acetylenes offers a route to "push-pull" substituted Dewar benzenes. If dimethyl acetylenedicarboxylate is added to a solution of *(1)* in THF at −65° C, the solution becomes deep red for a few seconds and then pale yellow. A yellowish oil can be isolated in 89% yield (n_D^{23} = 1.5033) which is shown to be a 1 : 1 adduct by elemental analysis and osmometric molecular weight determinations. Its thermal stability (it withstands prolonged heating to 100°C) and the ^{1}H-NMR spectrum (the ester ethyl groups differ only slightly from each other) would indicate structure *(9)*.



Similarly, *(1)* reacts with ethyl propiolate. The chemical shift of the ring-proton signal [τ = 2.0 (in $DCCl_3$)] reveals the aromatic character of the reaction product *(10)*. It may further be deduced from the ^{1}H-NMR spectrum that the adduct contains two equivalent ester groups and two equivalent diethyl amino groups and must therefore possess the structure *(10)*. It follows that the propiolate adds uniformly to *(1)*, and this in turn strongly suggests a dipolar intermediate or a highly polar transition state if steric effects are considered insignificant. – The symmetry of the adduct *(10)* provides further proof of the fact that the two diethylamino groups and the two ester groups in the cyclobutadiene *(1)* are not adjacent but occupy the 1,3 and 2,4 positions, respectively.

The Dewar benzene intermediate *(8)* could not be detected by NMR spectroscopy, even at as low a temperature as −46° C. The unusual instability of *(8)* compared to other Dewar ben-

zenes again underlines the limited value of orbital symmetry considerations for polar systems. The rapid valence isomerization of *(8)* to *(9)* can be explained by an HMO model developed by *H. U. Wagner*[5]. At room temperature *(1)* reacts with heterocumulenes to form six-membered cyclic 1 : 1 adducts *(11)*.

(1) + X=C=Y → 

(11)

Hetero-cumulene	*(11)* mp. (°C)	yield (%)	IR (cm^{-1})
C_6H_5NCO	100-101	85	1715, 1630, 1510, 1190
C_6H_5NCS	94	70	1730, 1580, 1500
$C_6H_5NCNC_6H_5$	114-116	78	1660, 1680, 1500
$(C_6H_5)_2CCO$	75	90	1679, 1650, 1600, 1560

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] *R. Gompper* and *G. Seybold*, Angew. Chem. *80*, 804 (1968); Angew. Chem. internat. Edit. *7*, 824 (1968).

[2] *R. Gompper* and *G. Seybold*, Angew. Chem. *83*, 44 (1971); Angew. chem. internat. Edit. *10*, 67 (1971).

[3] *H. Müller*, Dissertation, Universität Münster 1970.

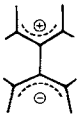
[4] *R. Gompper, W. Elsner*, and *H. Müller*, Angew. Chem. *79*, 473 (1967); Angew. Chem. internat. Edit. *6*, 453 (1967).

[5] *H. U. Wagner*, unpublished.

Detection of Dipoles in Cycloadditions to Allenes

By *Rudolf Gompper* and *Dietrich Lach*[*]

In conjunction with attempts[1] to detect and isolate dipoles of types *(1)* and *(2)* as intermediates of cycloadditions to allenes

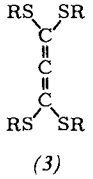


(1)

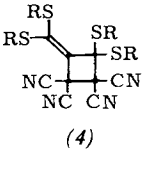


(2)

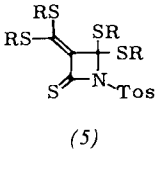
and heterocumulenes, we have studied the reaction of tetrakis(ethylthio)allene[2] *(3)*, as well as other "electron-rich" allenes, with tetracyanoethylene and with sulfonyl isocyanates and isothiocyanates. Since the adduct of tetramethoxyallene and tetracyanoethylene has recently been described[3], it is fitting that some of our experiments with *(3)* should also be reported. With the reactants mentioned above we obtained the 1 : 1 adducts *(4)–(8)* (see Table).



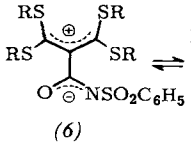
(3)



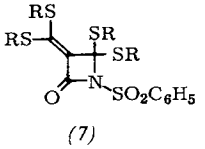
(4)



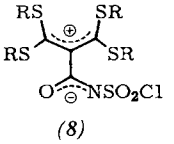
(5)



(6)



(7)



(8)

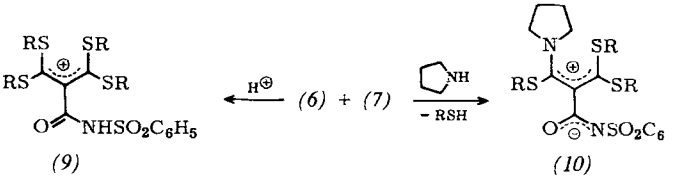
R = C_2H_5

Cpd.	^{1}H-NMR [a]	IR (cm^{-1})
(4)	8.67 (12H/M), 7.00 (8H/M)	2970 s, 2250 w, 1575 vs (KBr)
(5)	8.69 (12H/M), 7.05 (8H/M), 7.57 (3H/S), 2.67 (2H/D), 2.10 (2H/D)	2970 m, 1600 m, 1546 vs, 1533 vs (KBr)
(6) + *(7)*	8.80 (12H/T), 7.18 (8H/Q), 2.15 (5H/M)	2970 m, 1775 vs, 1610 s (KBr and $CHCl_3$)
(8)	8.54 (12H/T), 6.63 (8H/Q)	1630 s (Nujol)
(9)	8.54 (12H/T), 6.63 (6H/Q), 2.04 (5H/M)	1680 s ($CHCl_3$/HCl)
(10)	8.8 (3H/T), 8.75 (6H/T) 7.73 (4H/M), 7.10 (2H/Q), 7.07 (4H/Q), 6.29 (5H/M) 2.30 (5H/M)	2995 m, 1612 vs, 1590 vs, (KBr)

[a] TMS as internal standard, τ values in ppm, $DCCl_3$ as solvent ($DCCl_3/CF_3CO_2D$ for *(9)*).

The spectra of compounds *(4)* and *(5)* are consistent with the four-membered ring structure. The IR spectrum of the product of *(3)* and benzenesulfonyl isocyanate would also suggest a cyclic structure, *i. e. (7)*. However, such an assignment is contraindicated by the ^{1}H-NMR spectrum which shows only one quadruplet and one triplet for the ethylthio groups. If a solution of the product in $CDCl_3$ is cooled to −60° C, the quadruplet is replaced by two weakly structured signals at τ = 6.82 ppm and τ = 7.67 ppm (intensity ratio 1 : 1), the methyl proton peak at τ = 8.80 ppm becoming diffuse. It may therefore be concluded that at −60° C the four-membered ring *(7)* is present and at room temperature a fast equilibrium is set up between *(6)* and *(7)*, the mixture containing predominantly *(7)*. The solvent dependence of the ^{1}H-NMR spectrum of *(6)* + *(7)* indicates that the rate of interconversion *(6)*⇌*(7)* decreases in nonpolar solvents.

Acids protonate *(6)* + *(7)* to *(9)*; on treatment with pyrrolidine, ethanethiol is eliminated and the new dipole *(10)* results (see Table for spectra). Formation of *(10)* can be explained in terms of improved stabilization of the positive charge compared to *(6)*.



(9) *(10)*

R = C_2H_5

Action of chlorosulfonyl isocyanate on *(3)* gives only the dipole *(8)*, thus reflecting the superior stabilization of negative charge compared to the situation in *(6)*.

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[1] *R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. internat. Edit. *8*, 312 (1969).

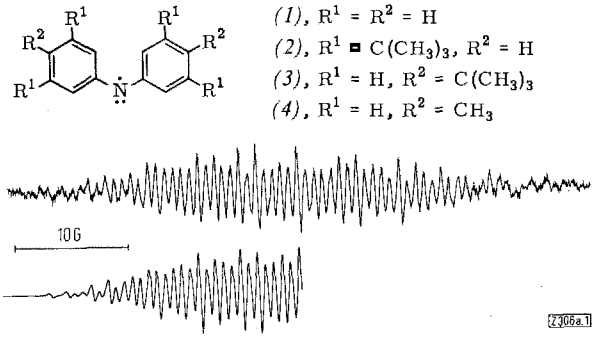
[2] *G. A. Wildschut, L. Brandsma*, and *J. F. Arens*, Recl. Trav. Chim. Pays-Bas *88*, 1132 (1969).

[3] *R. W. Hoffmann* and *W. Schäfer*, Angew. Chem. *82*, 700 (1970); Angew. Chem. internat. Edit. *9*, 733 (1970).

Diphenylaminyl[1]

By *Franz A. Neugebauer* and *Stephan Bamberger*[*]

Tetraphenylhydrazine dissociates into diphenylaminyl radicals *(1)* at 100° C or on irradiation with UV light[2]. Although the formation of *(1)* has been established by trapping with NO and triphenylmethyl[2], a well resolved ESR spectrum of this radical has hitherto not been obtained[3]. We have now recorded such a spectrum on irradiation of a 0.2 M solution of tetraphenylhydrazine in benzene with a 1000-W high-pressure mercury vapor lamp in a flow system (Fig. 1). The ESR spectra of the diarylaminyls *(2)* (Fig. 2), *(3)*, and *(4)* were also recorded under the



(1), $R^1 = R^2 = H$
(2), $R^1 = C(CH_3)_3$, $R^2 = H$
(3), $R^1 = H$, $R^2 = C(CH_3)_3$
(4), $R^1 = H$, $R^2 = CH_3$

Fig. 1. ESR spectrum of diphenylaminyl *(1)* in benzene (above); simulated spectrum (below) (line width 0.35 G).

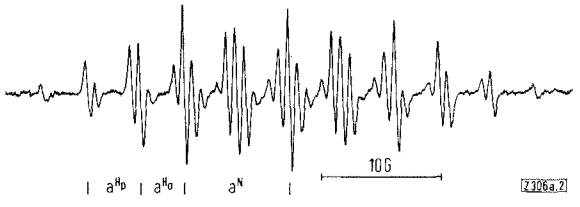


Fig. 2. ESR spectrum of bis(3,5-di-*tert*-butylphenyl)aminyl *(2)* in benzene.

same conditions. The ESR spectrum of *(4)* is identical with that obtained by thermal dissociation (90 °C) of tetra-*p*-tolylhydrazine[1].

Table 1. Coupling constants (in gauss) of the aminyls *(1)*, *(2)*, *(3)*, and *(4)* in benzene.

Cpd.	a^N	a^{H_o}	a^{H_m}	a^{H_p}
(1)	8.9	3.70	1.49	4.34
(2)	8.8	3.66	–	4.37
(3)	8.7	3.7	1.5	–
(4)	8.7	3.6	1.4	4.7 (H_{CH_3})

It may be calculated from the ESR coupling constants (Table 1) of diphenylaminyl[4,5,6] that the unpaired electron in diphenylaminyl is delocalized to the extent of about 60% into the phenyl groups (Table 2). In diphenylmethyl, the carbon analog of diphenylaminyl, about 66% of the spin density is localized on the methyl carbon[7]. This surprising result can be interpreted to some extent as a result of the higher electronegativity of the aminyl nitrogen. A quantitative interpretation is currently under investigation.

Table 2. Spin densities in diphenylaminyl *(1)*.

Position	Exp. [4,5] [a]	Calc. [6] [b]	[c]
N	0.311	0.3963	0.3682
C-1	–	-0.0066	0.0041
C-2, C-6	0.156	0.1306	0.1288
C-3, C-5	0.063	-0.0451	-0.0436
C-4	0.183	0.1375	0.1414

[a] $a^H = -23.7\varrho_C$; $a^N = 28.6\varrho_N$
[b] $\beta_{CN} = \beta_{CC}$, $\alpha_N = \alpha_C + 1.2\beta_{CC}$, $\lambda = 1.2$
[c] $\beta_{CN} = \beta_{CC}$, $\alpha_N = \alpha_C + 1.3\beta_{CC}$, $\lambda = 1.2$.

The hydrazines tetrakis(3,5-di-*tert*-butylphenyl)hydrazine (dec. pt. 259–261° C)[8] and tetrakis(4-*tert*-butylphenyl)hydrazine (dec. pt. 178–179° C)[8] were prepared by oxidation of bis(3,5-di-*tert*-butylphenyl)amine (m.p. 117–118° C)[8,9] and bis(4-*tert*-butylphenyl)amine (m.p. 104–105 °C)[8,9] with $KMnO_4$ in acetone.

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Diarylamine Radical Cations[1]

By *Franz A. Neugebauer* und *Stephan Bamberger*[*]

Oxidation of diarylamines in CF_3COOH with 0.5 equivalents of lead tetraacetate frequently gives intensely blue-colored solutions of diarylamine radical cations *(1)*, which we have now studied by ESR spectroscopy (Table). Because of the short lifetime of the diphenylamine radical cation *(1a)* its ESR spectrum was recorded in a flow apparatus (Fig. 1).



(1)



(2)

Table. Coupling constants of diarylamine radical cations *(1)* in CF_3COOH (in gauss).

Cpd.	Ar, substituents on phenyl	a^N	$a^{N_{NH}}$	a^{H_o}	a^{H_m}	a^{H_p}
(1a)	–	9.17	11.14	3.51	1.36	4.88
(1b)	4-CH_3	8.70	10.50	3.28	1.06	6.10 (CH_3)
(1c)	4-$(CH_3)_3C$	8.69	10.44	3.25	1.05	0.24 [$C(CH_3)_3$]
(1d)	3,5-$[(CH_3)_3C]_2$	8.64	10.50	3.36	–	5.15
(1e)	4-OCH_3	8.06	9.56	2.72	0.40	1.06 (OCH_3)
(1f)	2,6-$(CH_3)_2$, 4-OCH_3	7.05	8.61	1.73 (CH_3)	0.24	1.05 (OCH_3)
(1g)	2, 4, 6-$(OCH_3)_3$	7.41	9.15	0.59 (OCH_3)	0.43	0.76 (OCH_3)

The ESR spectrum of *(1e)* had already been observed upon dissolving bis(*p*-methoxyphenyl) nitroxide in CF_3COOH, but was assigned to the protonated nitroxide[2]. The observed $a^N/a^{H_{NH}}$ ratio of 0.84 provides support for our assignment. (For comparison: protonated 2,2,6,6-tetramethylpiperidine *N*-oxide: $a^N/a^{H_{NOH}} = 6.6$[3], *p*-phenylenediamine radical cation:

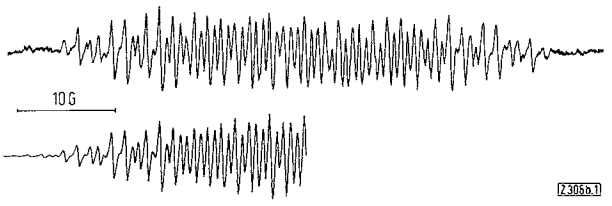


Fig. 1. ESR spectrum of diphenylamine radical cation *(1a)* in CF_3COOH (above); simulated spectrum (line width 0.3 G) (below).

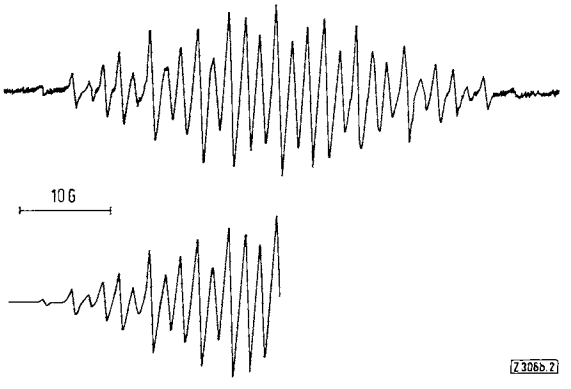


Fig. 2. ESR spectrum of bis(3,5-di-*tert*-butylphenyl)amine radical cation *(1d)* in CF_3COOH (above); simulated spectrum (below) (line width 0.5 G).

$a^N/a^{H_{NH}} = 0.9$[4], and $H_3\dot{N}^{\oplus}$: $a^N/a^{H_{NH}} = 0.73$[5].) Bis(*p*-methoxyphenyl) nitroxide disproportionates[6] in CF_3COOH and forms, among other products, the radical cation *(1e)*.

The diarylamine radical cations studied are representatives of a new series of secondary amine radical cations. They possess the same π-electron system as the diarylaminyls and can be regarded as protonated diarylaminyls. This is demonstrated by the ESR coupling constants of the parent systems diphenylaminyl[1] and *(1a)*, which differ only slightly from each other The calculated spin density distribution in diphenylaminyl[1] can also be used for *(1a)*.

Electron-donating substituents in the *para*- or *ortho*-position enhance the delocalization of the unpaired electron in *(1)* and decrease a^N. Bulky *ortho* substituents, which do not permit the π-system to achieve true planarity, have the opposite effect. In *(1f)* the electron-donating properties of the methyl group are more important than the opposing steric effect and the spin density on the nitrogen is lower than in *(1e)*. If the *o*-methyl substituents are replaced by the larger methoxy group then the steric effect predominates [*(1g),(1f)*].

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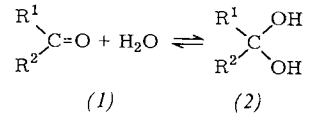
Diarylamine radical cations are derivatives of the extensively studied triarylamine radical cations *(2)*[7–11]. The coupling constants a^N of *(1)* are approximately 10% smaller than those of the corresponding *(2)* derivatives; the coupling constants of the ring substituents in *(1)*, however, are considerably larger than in the case of *(2)*[8]. In total, there is more spin density in the two aryl groups of *(1)* than in the three aryl groups of *(2)*. This apparently is due to an extensive twisting of the aryl groups of *(2)* about the N–C substituent axes.

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The Hydration Kinetics of 2-Methylbutyraldehyde

By *Marie-Luise Ahrens* and *Günter Maass*[*]

In aqueous solution many carbonyl compounds are in equilibrium with their hydrates[1]:



(1) *(2)*

(a), R^1 = H
R^2 = CH_3-CH_2-$CH(CH_3)$

A knowledge of the hydration behavior of simple carbonyl compounds, *e.g.* aliphatic aldehydes, permits conclusions to be drawn regarding the hydration behavior of more complex substances containing carbonyl groups.

Here, we report on the hydration behavior of 2-methylbutyraldehyde *(1a)*. Particularly useful information about the kinetics of hydration can be gained from a study of temperature jump – relaxation processes[2,3]. The change in absorption intensity of the characteristic carbonyl band can be used for the optical detection of the reaction *(1a)*$\rightleftharpoons$*(2a)* and for the determination of its equilibrium constants and their temperature dependence.

Equilibrium measurements: The ε_0^{max} of the 295 nm n-π^* band was determined for 2-methylbutyraldehyde in very dry tetrahydrofuran. Absorption obeyed the Beer-Lambert law and a molar extinction coefficient of $\varepsilon_0^{max} = 18.0\ l.mole^{-1}cm^{-1}$ was obtained. This value was used uncorrected for the investigations in aqueous solution. The absorption signal decreases because of hydrate formation; the equilibrium constant $K_{hydr.}$ = [hydrate]/[free aldehyde] can be determined from

$$E_{295} = \frac{\varepsilon_0^{max}}{1 + K_{hydr.}}\, c_0$$

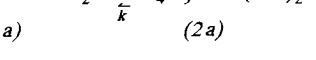
(E_{295} = measured extinction at λ = 295 nm, c_o = concentration by weight of aldehyde). Measurements at T = 22.0° C gave $K_{hydr.} = 0.43 \pm 0.05$.

The temperature dependence of the equilibrium *(1a)*$\rightleftharpoons$*(2a)* was determined by evaluation of the amplitudes of relaxation diagrams at various temperatures, these measurements were carried out with a temperature-jump apparatus for reactions in the seconds range[3]. A temperature jump ΔT causes a change ΔE in the extinction, and if a temperature independent value of ε_0^{max} is assumed, the following expression is valid:

$$\frac{d\ln K_{hydr.}}{dt} = \frac{\Delta H}{RT^2} = -\frac{(1 + K_{hydr.})}{K_{hydr.}} \cdot \frac{1}{\Delta T}\frac{\Delta E}{E_{max}} \qquad (1)$$

Measurements at T = 22.0° C yielded a value of $\Delta H = (-4.8 \pm 0.1)$ kcal/mole for the heat of hydration.

Kinetic measurements: The reaction



(1a) *(2a)*

is of pseudo-first order. The reciprocal relaxation time is given by the expression

$$1/\tau = \vec{k} + \overleftarrow{k} = \overleftarrow{k}\,(1 + K_{hydr.}) \qquad (2)$$

The measured rate of the hydration-dehydration reaction of 2-methyl-α-butyraldehyde is strongly dependent on the hydrogen ion and hydroxide ion concentration of the solution and on the concentration of any Lewis or Brönsted-type acids or bases that may be present. In this case a general acid-base catalysis occurs where the rate constants are given by:

$$\begin{aligned}\vec{k} &= \vec{k}_o + \vec{k}_H c_H + \vec{k}_{OH} c_{OH} + \sum_i \vec{k}_i c_i \\ \overleftarrow{k} &= \overleftarrow{k}_o + \overleftarrow{k}_H c_H + \overleftarrow{k}_{OH} c_{OH} + \sum_i \overleftarrow{k}_i c_i\end{aligned} \qquad (3)$$

The subscripts denote the catalysts (i = Lewis- or Brönsted-type acids or bases); k_o takes into account the contribution from possible intramolecular catalysis and catalysis effected by the solvent. The experimental conditions for the determination of the individual constants were chosen such that, in each case, one of the terms in eq. (3) was larger than the remaining terms. Two regions of linear dependence, corresponding to H^+ and OH^- catalysis (Fig. 1) respectively, are obtained on plotting log $1/\tau$ against pH from measurements carried out in presence of H^+ and OH^- ions and in the absence of general acids and bases.

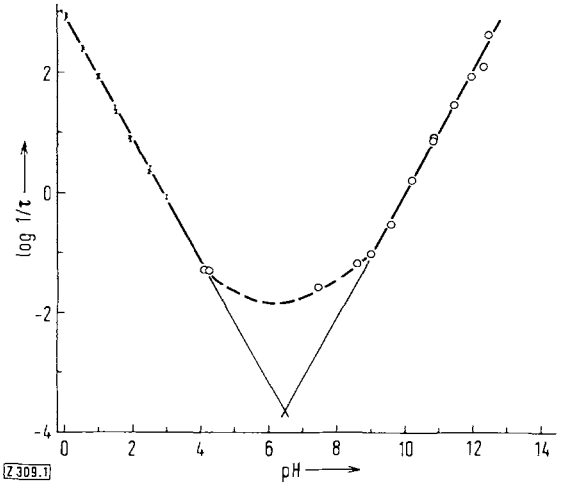


Fig. 1. Dependence of the relaxation time τ of the reaction *(1a)⇌(2a)* on pH. Adjustment of pH by addition of small amounts of HCl (x) or NaOH (o).

From these values the catalytic rate constants k_H and k_{OH} were determined with a mean error of 20% at $T = 22.0°$ C:

	hydration	dehydration
H^+catalysis:	$\vec{k}_H = 2.4 \times 10^2$ (l mole^{-1}s^{-1})	$\overleftarrow{k}_H = 5.7 \times 10^2$ (l mole^{-1}s^{-1})
OH^- catalysis:	$\vec{k}_{OH} = 4.5 \times 10^3$ (l mole^{-1}s^{-1})	$\overleftarrow{k}_{OH} = 1.2 \times 10^4$ (l mole^{-1}s^{-1})

Only limiting values can be given for k_0:

7.2×10^{-5} (s^{-1}) $\leq \vec{k}_0 \leq 0.4 \times 10^{-2}$ (s^{-1})

1.7×10^{-4} (s^{-1}) $\leq \overleftarrow{k}_0 \leq 1.1 \times 10^{-2}$ (s^{-1})

The following rate constants were determined for the acetic acid catalysis at $T = 22.0°$ C:

$\vec{k}_{Ac} = 0.5$ (l mole^{-1}s^{-1}) and $\overleftarrow{k}_{Ac} = 0.35$ (l mole^{-1}s^{-1})

The activation energies of hydration and dehydration as a function of temperature were obtained from kinetic measurements at pH = 4.22. Arrhenius plots (Fig. 2) of log $\vec{k}_H$ and log $\overleftarrow{k}_H$ against $1/T$ gives the following values for the activation energies $\vec{E}_A$ and $\overleftarrow{E}_A$ respectively: $\vec{E}_A = 6.9$ kcal/mole and $\overleftarrow{E}_A \approx 11.7$ kcal/mole.

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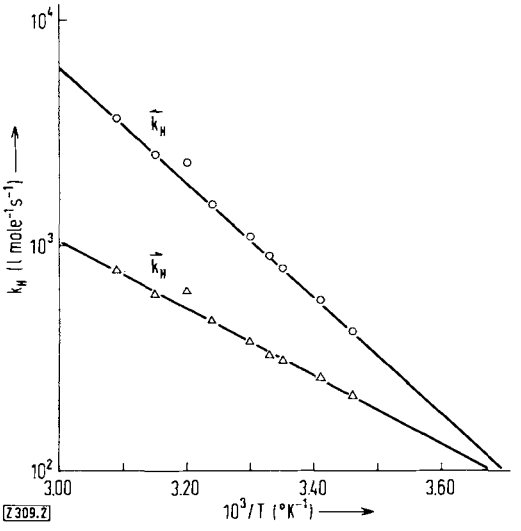


Fig. 2. Arrhenius plot of the results from a kinetic investigation of the reaction *(1a)⇌(2a)* at pH = 4.22.

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Tellurium Tetrachloride-Olefin Addition Compounds

By *H. J. Arpe* and *Herbert Kuckertz* [*]

Tellurium chlorides are the active components in catalyst systems for the oxychlorination and chlorination of olefins[1–3]. In this connection the most noteworthy reaction is the particularly smooth formation of allyl chloride from propene, which can be looked upon as a direct substitution reaction since 2-chloropropane and 1,2-dichloropropane are not formed as intermediates[1].

Addition of $TeCl_4$ to propene to give an analog of compound *(1)*, which is formed by reaction of $TeCl_4$ with ethylene, can be presumed as the primary step.

We have now checked whether similar addition compounds of propene and of butadiene exist and whether their thermal behavior reflects the result of oxychlorination of these olefins in the gas phase on tellurium catalysts.

Introduction of propene or butadiene into a 30% suspension of $TeCl_4$ in CCl_4 at 20–60°C leads to dissolution of $TeCl_4$ and separation of a yellow oil. Separation is complete on cooling the mixture to 0° C. Pure *(3)* and *(4)* (Table) can be isolated from the crude products in 20–30% yield by recrystallization from CCl_4. The reaction with ethylene is more sluggish and necessitates separation of the crystalline compounds *(1)* and *(2)* from unreacted $TeCl_4$ by CCl_4 extraction.
Supporting evidence for the composition of compounds *(1)–(4)* was provided by C,H,Cl,Te elemental analysis and by ^{1}H-NMR and IR spectroscopy. The X-ray structure analysis of *(2)* has

Table. Tellurium tetrachloride-olefin addition compounds.

No.	Adduct	M.p. (°C) (dec., uncorr.)
(1) [4]	$Cl_2Te(CH_2\text{-}CH_2Cl)_2$	111
(2)	$Cl_3Te\,CH_2\text{-}CH_2Cl$	116
(3) [5]	$Cl_2Te(C_3H_6Cl)_2$	100
(4)	$Cl_2Te(CH_2\text{-}CH{=}CH\text{-}CH_2Cl)_2$	83

already been carried out[6] whereas that of *(3)* has not, so a decision between the alternative structures $Cl_2Te(CH_2\text{-}CHCl\text{-}CH_3)_2$ and $Cl_2Te(CH(CH_3)\text{-}CH_2Cl)_2$ for *(3)* cannot as yet be made.

The adducts *(1)–(4)* are thermally unstable even below their melting points. The same products of thermolysis are formed as in the tellurium-catalyzed gas-phase process: *(1)* and *(2)* yield, alongside $TeCl_4$ and metallic tellurium, substantial amounts of ethylene and 1,2-dichloroethane and small amounts of vinyl chloride and HCl. Mainly allyl chloride, HCl, propene, and 2-chloropropane and a little 1,2-dichloropropane are formed in the decomposition of *(3)*. Compound *(4)* decomposes with formation of butadiene, HCl, butenyl chlorides, and high-boiling chlorohydrocarbons. There was no indication of chloroprene having been formed. Likewise, no free chlorine could be detected in the pyrolysis of *(1)–(4)*.

A further reaction affording olefin – analogous to a heterolytic fragmentation[7] – is the hydrolysis of *(1)–(4)* with dilute alkali or acid. It possibly limits the conversion of olefin in the gas-phase process[1].

(1)–(4) can be titrated with 0.5N NaOH and the liberated olefins determined volumetrically.

$$TeCl_4 \cdot (olefin)_n + 4NaOH \longrightarrow TeO_2 + 2H_2O + 4NaCl + n\ olefin$$

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X-Ray Crystallographic Investigations of Tellurium Tetrachloride-Olefin Adducts

By *D. Kobelt* and *E. F. Paulus*[*]

Passage of olefins such as ethylene or propylene through suspensions of $TeCl_4$ in CCl_4 at 20–60° C leads to an addition of one or two molecules of olefin, depending on the reaction conditions, to one molecule of $TeCl_4$[1]. We have determined the crystallographic data of $TeCl_4 \cdot 2C_2H_4$ *(1)* and $TeCl_4 \cdot 2C_3H_6$ *(3)* and carried out a three-dimensional X-ray structure analysis of $TeCl_4 \cdot C_2H_4$ *(2)*. 958 reflections were observed with a computer-controlled Siemens single-crystal diffractometer with MoK_α radiation according to the method proposed by *W. Hoppe*. After solving the structural problem and refining the parameters by the usual heavy atom method, an *R*-factor of 4.5% was obtained.

The Figure shows a projection of two $ClC_2H_4TeCl_3$ units on the *a/c* plane. The crystal contains polymer chains, whose structure is determined by mirror planes, glide planes, and two-fold axes. The tellurium atom has the coordination number 5. The ligands are at the corners of a pyramid having an approximately four-fold axis, the tellurium atom being situated very nearly in the center of the basal plane of the pyramid. The distance of the tellurium atom from the "best plane" through Cl-1, Cl-1′, Cl-2, Cl-2′ is 0.10 Å. The C-1–Te–Cl angles are 92.7 and 82.5°.

Table. Crystallographic data of tellurium tetrachloride-olefin addition compounds.

Compound	Cell constants						V (Å^3)	Z	$d_{x\text{-ray}}$ (g/cm^3)	Crystal system	Space group
	a(Å)	b(Å)	c(Å)	α(°)	β(°)	γ(°)					
$TeCl_4 \cdot 2C_2H_4$ *(1)*	7.87	12.50	10.51	90	106.5	90	991	4	2.18	monoclinic	$P2_1/c$
$TeCl_4 \cdot C_2H_4$ *(2)*	17.34	6.12	7.50	90	90	90	796	4	2.49	rhombic	Pcam
$TeCl_4 \cdot 2C_3H_6$ *(3)*	11.71	9.82	5.83	95.0	108.3	102.3	613	2	1.913	triclinic	P1 or $P\bar{1}$

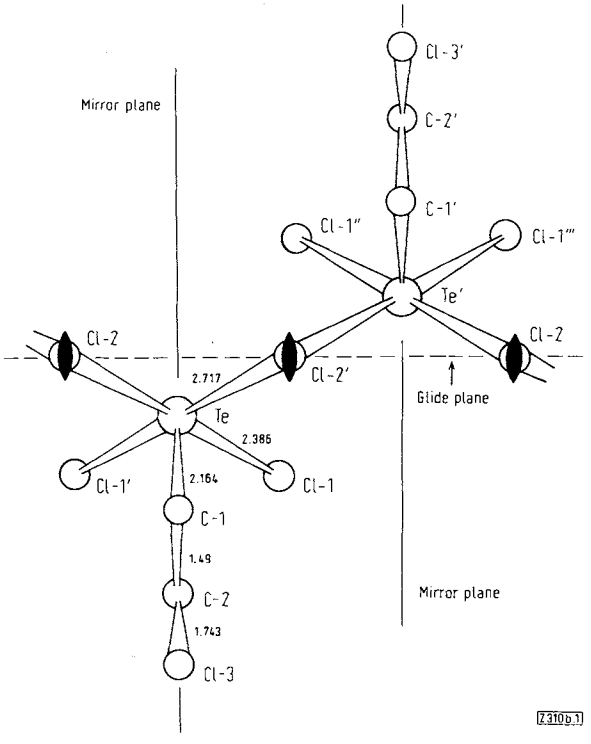


Fig. Crystal structure of β-chloroethyltellurium trichloride: Projection on the *a/c* plane. Standard deviation σ: Te-Cl 0.003, Te-C 0.013, C-C 0.02, C-Cl 0.014; lengths in Å.

The bridging chlorine atoms are about 0.3 Å further away from the tellurium than the terminal ones. This is much more pronounced in $TeCl_4$ (0.6 Å), which is tetrameric in the crystalline state and has a cubane-type structure with Te having a coordination number 6[2]; the Te-Cl distances of the terminal chlorine atoms have a value of 2.31 Å, and those of the bridging chlorine atoms 2.93 Å. A uniform value of 2.51 Å[3,4] was determined for the Te-Cl distance in $(CH_3)_2TeCl_2$, which crystallizes as monomer. To a good approximation one can assume the ions $TeCl_3^+$ and Cl^- in the case of $TeCl_4$[2] and four predominantly covalent bonds in the case of $(CH_3)_2TeCl_2$.

Compound *(2)*, having one Te-C bond, lies between $TeCl_4$, which has no Te-C bonds, and $(CH_3)_2TeCl_2$ which has two Te-C bonds; this explains the average Te-Cl distance of 2.38 Å for the terminal Cl atoms. According to this, Cl^- ions (on two-fold axis) and $ClCH_2$-$CH_2TeCl_2^+$ ions (on mirror plane) alternate along the polymer chain. Thus we find similar bonding characteristics as in TeF_4[5]. Separation into TeX_3^+ and X^- ions, however, seems to be indicated more prominently in our case. It appears to us to be unjustified to speak of a predominantly ionic lattice.

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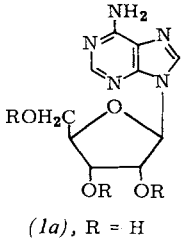
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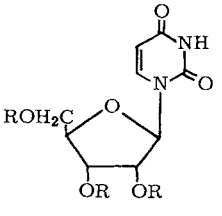
A Convenient Synthesis of 2',3',5'-Tri-*O*-acetyladenosine and -uridine

By *F. J. M. Rajabalee*[*]

A new method is described for the synthesis of 2',3',5'-tri-*O*-acetyladenosine *(1b)* and -uridine *(2b)*, *via* the boron trifluoride-catalyzed acetylation of adenosine *(1a)* and uridine *(2a)* respectively.



(1a), R = H
(1b), R = Ac



(2a), R = H
(2b), R = Ac

In a typical procedure, boron trifluoride-diethyl ether is added dropwise to a suspension of the nucleoside (1 part) in acetic anhydride (10 parts): the nucleoside soon dissolves in an exothermic reaction. The reaction mixture is allowed to stand at room temperature (adenosine: 1–2 h; uridine: 30 min)[1] after which it is co-evaporated with methanol (80 parts). The resulting syrup is dissolved in water (100 parts) and carefully neutralized with solid sodium bicarbonate. The filtered solution is then allowed to crystallize at 0 °C, giving after a few hours the chromatographically homogeneous triacetate *(1b)* or *(2b)*. *(2b)* can be recrystallized from absolute ethanol. *(1b)*, m.p. 166–167 °C, was thus obtained in 73–75% yield; *(2b)*, m.p. 129–130 °C, in 74–78% yield. Their identity was further confirmed by their undepressed melting points when admixed with authentic samples[2,3] and by their identical R_f values[1] and IR, UV, and NMR spectra.

The synthesis of *(1b)* and *(2b)* by the present method offers certain advantages over the pyridine-catalyzed method[2,3]: it is faster, gives a purer product (even the "crude" acetylated product obtained is chromatographically homogeneous whereas recrystallization is always required in the pyridine-catalyzed procedure) and yields are higher. Nucleoside acetates *(1b)* and *(2b)* are useful intermediates; they are, for instance, excellent substrates for reaction with triethyloxonium tetrafluoroborate (Meerwein reagent) in dichloromethane (both being soluble in that solvent), leading to *N*-ethylated nucleosides, which command interest in cancer research.

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[1] The progress of the reaction is monitored by thin layer chromatography on Silica Gel GF 254, using chloroform-methanol (5 : 1) as irrigating system.

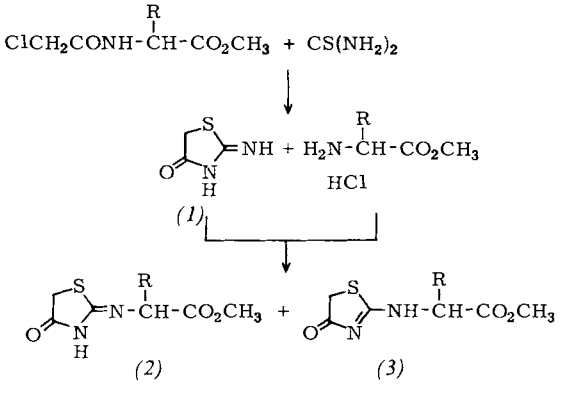
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Removal of the Chloroacetyl Group from *N*-Chloroacetyl Derivatives of Amino Acids and Peptides by Means of 1-Piperidinethiocarboxamide[**]

By *Wolfgang Steglich* and *Hans-Georg Batz*[*]

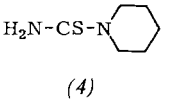
It has recently been found that the *N*-chloroacetyl group can readily be removed with thioureas[1,2]. However, the amines are often obtained from the *N*-chloroacetyl-peptide derivatives in only unsatisfactory yields owing to a secondary reaction that we have studied in the case of the methyl ester of *N*-chloroacetyl-L-valine. If this compound is treated with thiourea in the usual way, thin layer chromatography of the product indicates the presence of not only the methyl ester of valine and *(1)* but also compounds *(2)* and *(3)*, which are also formed on reaction of *(1)* with valine methyl ester hydrochloride in boiling water[3,4].



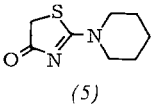
(1)

(2) *(3)*

This secondary reaction can be avoided if an *N*, *N*-disubstituted thiourea, such as 1-piperidinethiocarboxamide (*N*, *N*-pentamethylenethiourea) *(4)*[5] is used in place of thiourea. The *N*-chloroacetyl residue is then removed quantitatively after several hours' boiling in ethanol without any reaction occurring between the resulting 2-piperidinothiazolin-4-one *(5)* and the amine.



(4)



(5)

This reaction greatly enhances the utility of the *N*-chloroacetyl group as a protecting group for peptide syntheses. Thus *N*-chloroacetyl-Val-Val-OtBu (m.p. 132–134 °C; [α] = –65.1 °[6]) affords *N*-chloroacetyl-Val-Val-Val-OtBu (m.p. 210–211 °C; [α] = –89.6°) in 91% yield after removal of the chloroacetyl group with *(4)* and reaction with *N*-chloroacetyl-Val by the dicyclohexylcarbodiimide/hydroxysuccinimide method[7]. Similarly, *N*-chloroacetyl-Ile-Val-OtBu (m.p. 100–103 °C; [α] = –68.3°) affords TFA-Ile-Leu-Val (yield 69%; m.p. 220–222 °C; [α] = –84.6°) after removal of the protecting group, coupling with TFA-Ile, and removal of the *tert*-butyl group with trifluoroacetic acid. According to the ^{19}F-NMR spectrum the compound is optically pure[8].

The *N*-chloroacetyl group is also well suited for protection of the ω-amino functions of ornithine and lysine. N^{α}-TFA-N^{δ}-chloroacetyl-Orn-Leu-OtBu (m.p. 149–152 °C; [α] = –38.8°) is converted into N^{δ}-chloroacetyl-Orn-Leu-OtBu (yield 98%) by treatment with $NaBH_4$/ethanol[9]; this compound then gives TFA-Ile-N^{δ}-chloroacetyl-Orn-Leu-OtBu (yield 58%; m.p. 194–197 °C; [α] = –61.5°) on reaction with TFA-Ile-OSu. Treatment with *(4)* and removal of the ester group with trifluoroacetic acid furnishes TFA-Ile-Orn-Leu (as trifluoroacetate: yield 73%; m.p. 191–193 °C; satisfactory amino acid analysis). The dipeptide derivative obtained from *N*-chloroacetyl-Val and Val-OtBu according to the dicyclohexylcarbodiimide/hydroxysuccinimide method showed no racemization in the Weygand test[10] after removal of the chloroacetyl group with *(4)* and conversion into the TFA-dipeptide methyl ester.

Procedure:

N-Chloroacetyl-peptide ester (10 mmoles), compound *(4)* (12 mmoles), and glacial acetic acid (0.5 ml) are refluxed for 2–5 h in anhydrous ethanol. After addition of methyl chloroacetate (2.5 mmoles) the reaction mixture is boiled for a further hour in order to convert the excess of *(4)* into *(5)*, the ethanol is removed under vacuum, and the residue is partitioned between saturated aqueous K_2CO_3 solution and ethyl acetate. The organic phase is washed three times with water, dried, and evaporated down. Compound *(5)*, which does not interfere with the next peptide coupling step, is subsequently removed by extraction with acid.

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[**] This work was supported by the Bundesministerium für Wissenschaft und Forschung.

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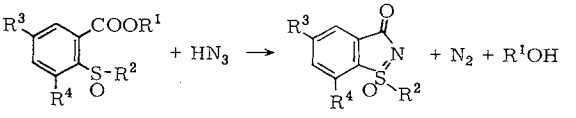
3-Oxobenzo[*d*]isothia(IV)-azole 1-Oxides

By *Peter Stoss* and *Gerhard Satzinger*[*]

The reaction of sulfoxides with hydrazoic acid leads to sulfoximides[1,2].



If esters of 2-sulfinylbenzoic acids *(1)* are used as starting materials then ring closure occurs simultaneously to give cyclic sulfoximides. These 3-oxobenzo[*d*]isothia(IV)-azole 1-oxides *(2)* are representatives of a new heterocyclic system.



(1) *(2)*

	R^2	R^3	R^4	*(1)* [a] m.p. (°C)	yield (%)	*(2)* m.p. (°C)	yield (%)	IR (cm^{-1}) in KBr NSO
(a)	CH_3	H	H	66-67	88	210-211	85	1227, 1124, 995
(b)	*n*-C_4H_9	H	H	oil	80 [b]	119	14	1247, 1220, 1124, 98
(c)	C_6H_5	H	H	84-85	68	127-128	37	1232, 1205, 1105, 97
(d)	CH_3	Cl	H	86	70	194	23	1235, 1205, 1124, 98
(e)	CH_3	Cl	Cl	oil	84 [b]	215	15	1245, 1227, 1000

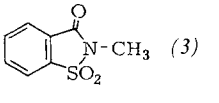
[a] $R^1 = CH_3$.
[b] Crude product.

The conversion of *(1)* into *(2)* is carried out under the conditions of the Schmidt reaction. Polyphosphoric acid is suitable both as acid catalyst and as solvent. Toluene, chlorobenzene, and dichloroethane, as well as other solvents, may, however, also be used as diluents.

The sulfoxides *(1)* can be obtained by oxidation of the corresponding sulfides with sodium periodate.

The new ring system exhibits exceptional chemical stability. For example, compound *(2a)* is unaffected by hot concentrated sulfuric acid and by 48 hours' refluxing with 1N ethanolic KOH.

The carbonyl frequencies of compounds *(2)* (1675–1686 cm^{-1}) are remarkably low compared to those of 2-methyl-3-oxo-1,2-dihydrobenzoisothiazole 1,1-dioxide *(3)* (1730 cm^{-1}). The typical sulfoximide bands (NSO frequencies) occur at about the same wavelengths as those of *N*-alkyldiphenylsulfoximides[3]. The UV spectra of *(3)* and, *e. g.*, *(2a)* are very similar:



(3)

(3) (CH_3OH): $\lambda_{max}(\varepsilon) = 295$ (905); 285; 253 nm;
(2a) (CH_3OH): $\lambda_{max}(\varepsilon) = 294.5$; 285 (1300); 278.5 nm.

1-Methyl-3-oxobenzo[d]isothia(IV)-azole 1-oxide (2a)

Methyl 2-methylsulfinylbenzoate *(1a)* (99 g, 0.5 mole) is added to a mixture of 85% phosphoric acid (500 g) and phosphorus pentoxide (250 g) and the whole is heated to 80° C. Sodium azide (39 g, 0.6 mole) is then added to the reaction mixture at this temperature with vigorous stirring over a period of 2 hours. Stirring is continued for another 4 hours at the same temperature and the mixture is then cooled, diluted with water (500 ml), and neutralized with aqueous potassium hydroxide. The product *(2a)* can then be filtered off with suction (yield 77 g, 85%, recrystallized as colorless crystals from water).

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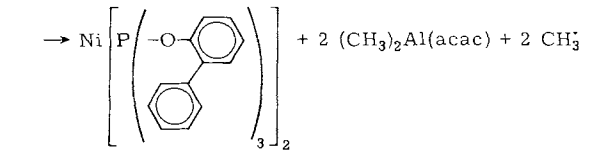
Bis(tri-2-biphenylphosphite)nickel

By *M. Englert, P. W. Jolly,* and *Günther Wilke*[*]

In continuation of our studies on the chemistry of coordinatively unsaturated nickel complexes[1–3] we wish to report the preparation and some reactions of bis(tri-2-biphenylphosphite)-nickel, *(1)*.

It has been previously reported that the reduction of bis(2,4-pentanedionato)nickel(II) (nickel acetylacetonate, $Ni(acac)_2$) in the presence of tri-2-biphenylphosphite (hereafter referred to as L) by a large excess of trimethylaluminum leads to formation of $L_2Ni(CH_3)_2$[4]. Using a stoichiometric amount of trimethylaluminum the reaction takes a different course and *(1)* may be isolated as an orange solid in over 90% yield.

$$Ni(acac)_2 + 2\ P(OC_6H_4\text{-}o\text{-}C_6H_5)_3 + 2\ Al(CH_3)_3$$



$$+ 2\ (CH_3)_2Al(acac) + 2\ CH_4$$

(1)

The composition of *(1)* is confirmed by the reaction with monoolefins to give the corresponding olefin complexes[5] and by the absorption of two molecules of CO per molecule of complex with formation of $L_2Ni(CO)_2$.

In solution (toluene) *(1)* is dissociated and shows the expected catalytic activity with butadiene[6]. If the reaction with *(1)* is carried out below room temperature the butadiene complex *(2)* may be isolated. *(2)* is also formed by the thermal rearrangement of the olefin complex *(3)* formed from *(1)* and methylenecyclopropane.



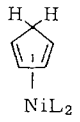
(2) *(3)*

(1) trimerizes allene forming 1,2,4-trimethylenecyclohexane *(4)* and a bis-π-allyl-C_9 NiL compound. A complex containing an open chain dimer is obtained from the corresponding reaction with dimethylallene.

Reaction of *(1)* with cyclopentadiene yields the complex *(5)*, which, in contrast to the corresponding bis(tricyclohexylphosphane)nickel derivative[3], shows no tendency to form a cyclopentadienylhydridonickel complex. This is also the case



(4)



(5)

for the reaction with acetic acid from which a derivative of nickel(I) – $L_2Ni^{I}OC(O)CH_3$ – is obtained with the simultaneous evolution of one equivalent of hydrogen.

Other less sterically demanding phosphanes add to *(1)* forming mixed nickel phosphane complexes. For example tricyclohexylphosphane adds to form the bright red $L_2Ni(P(C_6H_{11})_3$ which may also be formed by reacting bis(tricyclohexylphosphane)-nickel[1,2] with tri-2-biphenylphosphite.

Attempts to prepare other bis(ligand)nickel complexes have so far met with no success and we attribute the formation of the molecule *(1)* to steric factors and to a shielding of the central atom by the six *o*-phenyl groups which can be clearly seen from molecular models.

Experimental

$Al(CH_3)_3$ (20 mmole) in pentane (5 ml) is dropped slowly into a solution of $Ni(acac)_2$ (5.1 mmole) and tri-2-biphenylphosphite (10.2 mmole) in ether (200 ml) cooled to −60 °C. The mixture is allowed to reach room temperature and stirred for 14 hours. The resulting bright orange precipitate is filtered off and washed with ether in which it is insoluble. Yield > 90%.

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CONFERENCE REPORTS

Triplet Biradicals in Cycloaddition

By *Paul D. Bartlett*[*]

Photosensitized cycloaddition is known to originate in energy transfer from an excited triplet state of the sensitizer to that participant in the cycloaddition with the most favorable triplet excitation energy. Such a reaction can serve as a reference model of the behavior of a biradical intermediate.

Losses of configuration from an alkene during cycloaddition are the result of rotations occurring about single bonds during the lifetime of an intermediate biradical. Even in singlet biradicals extensive configuration loss occurs while a conformation suitable for ring closure is being approached; in triplet biradicals the lifetime of intermediate biradical. Even in singlet biradicals extensive configuration loss occurs while a conformation suitable for ring closure is being approached; in triplet biradicals the lifetime is further increased by the need for an electron spin inversion before a bond can be formed.

Thermal cycloaddition of *cis*- or *trans*-2-butene to cyclopentadiene yields 1,4-addition products stereospecifically; photosensitized reaction yields a mixture of three 1,4- and four 1,2-cycloadducts.

Complete identifications an quantitative analyses have been made of the product mixtures from *cis*- and *trans*-2-butene *(B. D. Kramer)*, *cis*- and *trans*-1,2-dichloroethylene *(O. A. Wersel)*, *cis*- and *trans*-1,2-dichloro-1,2-difluoroethylene *(R. Wheland)*, and *cis*- and *trans*-1-chloropropene *(L. A. Hull)*, in photosensitized addition to cyclopentadiene. Extensive loss of configuration occurs in all cases, but the product mixtures from *cis* and *trans* olefins remain different in serveral respects:

(1) The diastereomeric biradicals are formed to a greater extent in the *threo* configuration from the *trans* than from the *cis* alkenes;

(2) *Trans* alkenes produce consistently higher proportions of 1,4- to 1,2-adducts than do their *cis* isomers (with 2-butene this is not apparent at 30 °C but becomes so at −15 °C);

(3) In six out of ten cases, pairs of 1,2-cycloadducts formed competitively from the same biradical show a "crossover" phenomenon such that the *cis/trans* ratio is higher from *trans* alkene than from *cis*- by factors up to 4. The "crossover" being absent in the 1,4-adducts, it is proposed that

(a) the most favored initial conformation of the biradical is that appropriate to 1,4-ring closure, and retains the original configuration of the olefin,

(b) rotation from this conformation to that preceding 1,2-ring closure is coupled with an inversion from *cis* to *trans* or vice versa,

(c) there is a net flow of biradicals from the 1,4- to the 1,2-conformation, which superposes a net "crossover" on the general stereochemical equilibration resulting from the long life of the triplet biradicals. The coupling of rotations may be mechanical and highly specific, or it may have a general orbital basis analogous to the compulsory inversion in a 1,3-sigmatropic rearrangement.

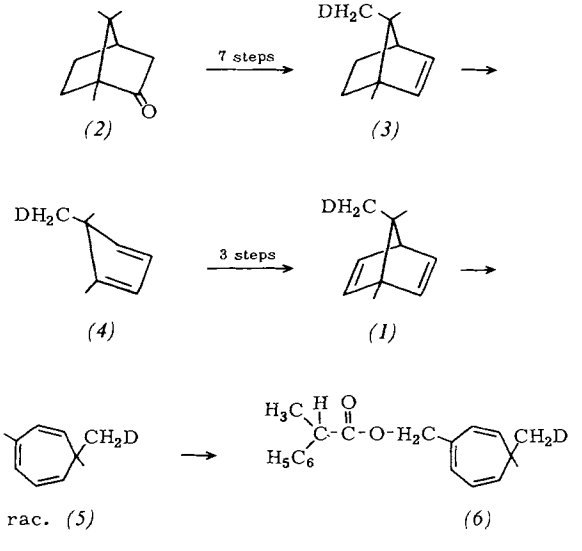
Lecture at Mülheim/Ruhr on September 14, 1970 [VB 259 IE]
German version: Angew. Chem. *83*, 49 (1971)

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Chiral Bornadiene: Its Synthesis and Rearrangement

M. R. Willcott, III and *C. J. Boriack*[*]

Bornadiene (1,7,7-trimethylbicyclo[2.2.1]hepta-2,5-diene) is converted to 3,7,7-trimethyltropilidene (3,7,7-trimethyl-1,3,5-cycloheptatriene) and *p*-cymene in the gas phase between 220 and 300 °C. Trimethyltropilidene is formed in a first order process with the rate $k = 10^{13.94} e^{-40.6/RT} s^{-1}$. Since these parameters do not give any accurate indication of the mechanism, a study of chiral (-)-(7*R*)-8-deuteriobornadiene *(1)* was undertaken. The chiral compound was prepared from (+)-camphor *(2)* in 11 steps in good overall yield. The most likely racemization step in the synthesis, the conversion of [D]-bornylene *(3)* to [D]-1,5,5-trimethylcyclopentadiene *(4)*, was monitored by the appearance of deuterium in the allylic methyl group. At a later point in the synthesis, the optical purity of [D]-bornadiene is determined in a simple NMR experiment from intensity measurements of the CH_3 and CH_2D groups. In this way, [D]-bornadiene was shown to be 82% enantiomerically pure.



Pyrolysis of [D]-bornadiene in the gas phase produced a [D]-trimethyltropilidene *(5)* of unknown optical purity. After a number of unsuccessful attempts to measure the optical purity, we found that conversion of the 3-methyl group to the hydratropyl ester derivative *(6)* from optically pure acid made a molecule in which the two 7-Methyl groups were measurably diastereotopic. Determination of the amount of deuterium in each methyl resonance permitted us to conclude that the [D]-trimethyltropilidene was racemic.

The mechanism of the rearrangement must involve either a symmetrical transition state, or a symmetrical high energy intermediate. It is possible that the role of the *p*-cymene can help in deciding between the transition state and the intermediate.

Lecture at Marburg, December 4, 1970 [VB 262 IE]
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The Influence of the Complexed Metal Ion on the Mass Spectra of Organic Metal Complexes

By *Herbert Budzikiewicz*[*]

The fragmentation behavior of analogous organic compounds differing only in the nature of a hetero atom is influenced by this hetero atom. There are similar differences in the degradation reactions of organometal complexes and those of the uncomplexed ligand which may depend further upon the metal present in the complex. To explain this various factors have been invoked, such as

a) the nature of the bond (*e.g.*, metallocenes),

b) charge localization in the molecular ion on the ligand or on the metal (*e.g.*, benzenetricarbonylchromium derivates or pentanedionates),

c) possible change of valency of the complexed metal (*e.g.*, pentanedionates),

d) steric factors.

In order to investigate the importance of these various factors porphyrin complexes as well as model compounds were used. Simple porphin derivatives fragment – both starting from M^+ and from M^{2+} – preferentially in a way that even electron daughter ions are formed. This mode of fragmentation is retained with all metal complexes investigated and one may conclude that the positive charge and hence the radical site in the molecular ion is stabilized by the aromatic π-system and not by the complexed metal so that possible changes of valency are of no major importance. This conclusion is confirmed by the observation that the fragmentation behavior of the analogous metal complexes of 2-butyl-8-hydroxyquinoline, which exhibits a less extended π-system than the porphyrins, depends upon the ability of the complexed metal to change its valency. These quinoline complexes occupy an intermediate position between those of porphin derivatives and pentanedionates. The fragmentation pattern of more highly substituted porphyrins and chlorins may differ greatly from that of their complexes, which can be explained by assuming differing interatomic distances as well as changed steric relationships in the overcrowded part of the molecule.

Lecture at Leverkusen on September 24, 1970 [VB 260 IE]
German version: Angew. Chem. *83*, 85 (1971)

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Adsorption of Oxygen on Gold and its Effect on the Kinetics of Electrochemical Reactions

By *Gerhard M. Schmid*[*]

At potentials greater than 1.25 V the adsorption of oxygen on gold in 1 M H_2SO_4 or 1 M $HClO_4$ increases linearly with potential, monolayer formation being complete (two electrons per surface atom) at 1.45 V. At 1.70 V a second monolayer has formed. The adsorption exhibits hysteresis: oxygen that has been adsorbed between 1.25 and 1.70 V is only removed from the surface at potentials $\leq$ 1.25 V. Moreover, no difference could be detected between the first and the second monolayer. In acidic solutions containing chloride ion, the dissolution current of gold going into solution as $AuCl_4^-$ is directly proportional to the oxygen-free surface area. On formation of an oxygen monolayer dissolution ceases and the electrode is passive. On the other hand, the adsorbed oxygen reduces the apparent rate constant of the Ce^{III}/Ce^{IV} reaction in 1 M H_2SO_4 only from 12×10^{-4} cm/s (free surface) to 3×10^{-4} cm/s (monolayer). The rate constant remains unchanged when the coverage is increased to two monolayers. The charge transfer coefficient, $\alpha = 0.65$, is independent of the oxygen coverage. The change in the rate constant can be explained by a change of the potential drop in the inner double layer by 8mV. It would appear that the adsorbed oxygen is incorporated into the metal lattice, is a good electron conductor, and has only a slight effect on the potential conditions in the inner double layer.

Lecture at Mainz on September 15, 1970 [VB 258 IE]
German version: Angew. Chem. *83*, 49 (1971)

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SELECTED ABSTRACTS

Surface tension and compressibility of liquids near their triple points conform to a simple relation according to *P. A. Egelstaff* and *B. Widom*. On inspection of 30 liquids (*e.g.*, K, Ag, NaBr, N_2, H_2O, chlorobenzene) it was observed that while the surface tension and the compressibility separately vary by a factor of 150 their product varies only by a factor of about 3; its value always amounts to some tenths of an ångström unit. With the aid of a statistical model it is shown that this product, apart from a constant factor, corresponds to the "surface layer thickness", *i.e.* the depth below the surface where the intensive properties of the liquid no longer differ from those in the bulk. Apparently this distance is only weakly dependent on the nature of the intermolecular forces./J. Chem. Phys. *53*, 2667 (1970)/–Hz.

[Rd 259 IE]

The dipole moments of the diatomic IV/VI molecules (*e.g.*, CO, GeSe) are reported comprehensively by *J. Hoeft, F. J. Lovas, E. Tiemann,* and *T. Törring*. The dipole moments were evaluated mostly from Stark effect measurements on rotational transitions in the microwave spectrum. A plot of dipole moments *versus* internuclear distances reveals that molecules with one common atom are located on straight lines; this relation allows the prediction of internuclear distance and dipole moment for molecules not yet investigated, *e.g.*, for SiTe. This simple relation between dipole moment and internuclear distance in this class of molecules is in clear disagreement with the corresponding data of the alkali metal halides. For SnS, the dipole moments of the four lowest excited vibrational states are also reported./J. Chem. Phys. *53*, 2736 (1970)/–Hz.

[Rd 260 IE]

The vibrational frequencies of adsorbed SO_2 are reported by *M. A. K. Phillips* and *R. C. Seymour*. The low frequency IR spectra were measured by Fourier analysis of interferograms. CsCl films were prepared by evaporation of CsCl onto polyethylene sheets at −196 °C and subsequent annealing at −78 °C. Specific surface areas of these films were found to be in excess of 200 m^2/g. On adsorption of SO_2 at a pressure of 0.1 torr a broad absorption band centered at 220 cm^{-1} appears. Its intensity increases with increasing SO_2 pressure. At 1 torr, a second band appears at 308 cm^{-1}. On evacuation, the 220 cm^{-1} band disappears rapidly, whereas the 308 cm^{-1} band requires continuous pumping for several hours to vanish. The band at 220 cm^{-1} is considered to be due to the vibration of physically adsorbed SO_2 molecules perpendicular to the surface, whereas the 308 cm^{-1} band is ascribed to a chemisorbed species formed by interaction of SO_2 with ions in the surface./Chem. Phys. Lett. *6*, 553 (1970)/–Hz.

[Rd 261 IE]

***N-tert*-Butyliminoacetonitrile** *(3)*, the first representative of a new group of compounds, the iminoacetonitriles RN=CHCN, has been synthesized by *J. H. Boyer* and *H. Dabek*. *N-tert*-Butylaminoacetonitrile *(1)* is converted by reaction with *tert*-butyl hypochlorite into *N*-chloro-*N-tert*-butylaminoacetonitrile *(2)*, whose dechlorination by triethylamine affords compound *(3)* (b.p. 28–29 °C/3 torr) in 46% yield. Catalytic reduction of *(3)*

$$\underset{(1)}{tBu\text{-}NH\text{-}CH_2CN} \longrightarrow \underset{(2)}{tBu\text{-}NCl\text{-}CH_2CN} \longrightarrow$$

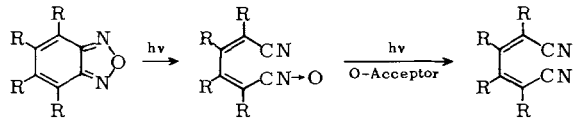
$$\underset{(3)}{tBu\text{-}N{=}CHCN} \xrightarrow[SiO_2]{HCN} tBu\text{-}NH\text{-}CH(CN)_2 \xrightarrow[SiO_2]{(3)}$$

$$tBu\text{-}NH\text{-}\overset{\overset{CN}{|}}{\underset{\underset{CN}{|}}{C}}\text{—}\overset{\overset{H}{|}}{\underset{\underset{CN}{|}}{C}}\text{-}NH\text{-}tBu \quad (4)$$

with W-2 Raney nickel gives *N-tert*-butylethylenediamine. *(3)* can be partly converted on a silica gel column into 1,2-di-*tert*-butylamino-1,1,2-tricyanoethane *(4)*, which is probably formed from HCN and two molecules of *(3)*./Chem. Commun. *1970*, 1204/-Ma.

[Rd 262 IE]

The preparation of 1,2-dinitriles from furazanes by UV irradiation in the presence of a reducing agent (triethyl phosphite) is the subject of a report by *T. Mukai* and *M. Nitta*. The nitrile oxide group formed in the intermediate is reduced to the nitrile group. Benzofurazane *(1)*, R = H, gives *cis,cis*-1,4-dicyano-1,3-butadiene *(2)*, R = H (80% yield), along with the *cis,trans* and *trans,trans* isomers (in 2% and 3.5% yields resp.). Naphthofurazane affords *cis*- and trans-*o*-cyanocinnamonitriles in 45% and 35% yields resp. Phenanthrofurazane is converted into 2,2'-

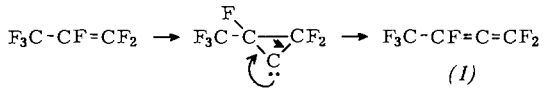


(1) (2)

dicyanobiphenyl. The photocleavage possibly proceeds *via* the singlet state of the furazane. / Chem. Commun. *1970,* 1192/-Ma.

[Rd 263 IE]

Fluorinated allenes, which have previously only been accessible by multistep syntheses, have been prepared by *M. J. McGlinchey, T. Reynoldson,* and *F. G. A. Stone* by reaction of carbon vapor (generated in an electric arc) with compounds $CF_2=CFX$ (X = CF_3, Cl, Br). For example, perfluoropropene gives perfluoro-1,2-butadiene *(1),* b.p. −5° C, in 20% yield;

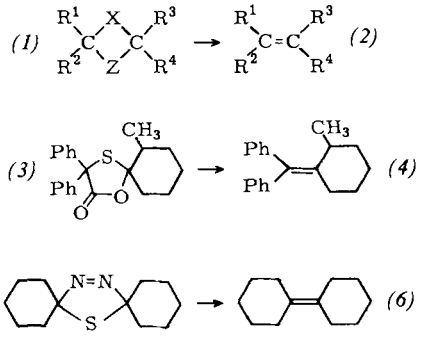


(1)

chlorotrifluoroethylene analogously gives $ClFC=C=CF_2$, b.p. 12.6°C, in 10–15% yield. Reaction of bromotrifluoroethylene with carbon vapor leads to only *ca.* 5% $BrFC=C=CF_2$ along with 1-bromo-2,3,3-trifluorocyclopropene. The allene formation presumably proceeds *via* cyclopropylcarbene intermediates. / Chem. Commun. *1970,* 1264/-Ma.

[Rd 264 IE]

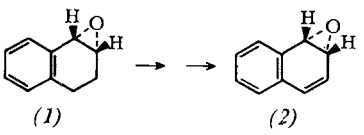
A novel method for olefin synthesis by double elimination has been developed by *D. H. R. Barton* and *B. J. Willis,* namely *(1)*→ *(2),* in which R^1, R^2 ... are alkyl, aralkyl, aryl, *etc.* and X and Y are residues that are easily eliminated. The CC double



bond is formed intramolecularly. The method is suitable for the synthesis of sterically hindered olefins. Thus, *e.g.,* the 1,3-oxathiolan-5-one *(3)* obtained by condensation of thiobenzilic acid, $Ph_2C(SH)COOH$, with 2-methylcyclohexanone is converted into the olefin *(4)* to the extent of 81% on being heated in presence of tris(diethylamino)phosphane. A further example is the synthesis of bicyclohexylidene *(6)* by heating *(5)* in presence of triphenylphosphane. Photolysis of the thiadiazole *(5)* does not yield olefin. / Chem. Commun. *1970,* 1225, 1226/-Ma.

[Rd 265 IE]

Optically active 1,2-naphthalene oxide *(2)* has been synthesized by *D. R. Boyd, D. M. Jerina,* and *J. W. Daly* from 1,2-epoxy-1,2,3,4-tetrahydronaphthalene *(1)* by conversion into the 4-bromo derivative, from which HBr was subsequently eliminated. (−)-*(1)* gave (−)-*(2)* in about 10% optical purity. Compound *(2),* which rapidly isomerizes to naphthol in methanol at 50° C, is optically and chemically stable at −80° C; at 20° C it can be kept for 25 h in $CHCl_3$ and for 8 h in CH_3OH. Addition of a trace of acetic acid to a methanolic solution of *(2)* leads

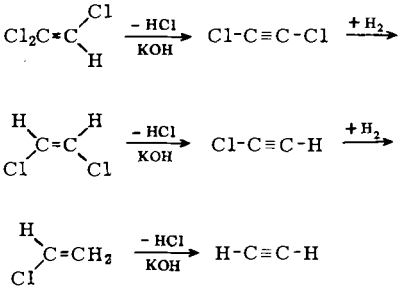


(1) (2)

to complete loss of optical activity within 1.5 h and to formation of naphthol; addition of a little methanolic KOH effects racemization without isomerization to naphthol. / J. Org. Chem *35,* 3170 (1970)/-Kr.

[Rd 266 IE]

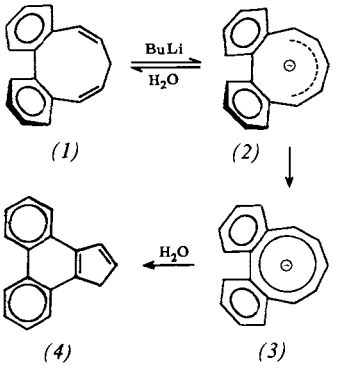
A safe synthesis of dichloroacetylene is described by *J. Siegel, R. A. Jones,* and *L. Kurlansik;* the reaction is carried out in ethylene glycol as solvent instead of in a dry combustion tube filled with NaOH as previously. Moreover, an excess of ether, which is known to delay the autoxidation of dichloroacetylene, is present throughout the reaction. The formulas illustrate the



formation of Cl–C≡C–Cl and indicate possible modes of by-product formation. The acetaldehyde found could arise from the ether or from the ethylene glycol. / J. Org. Chem. *35,* 3199 (1970)/-Kr.

[Rd 267 IE]

The anions of dibenzo[c,e]cyclononene *(1)* are the subject of a paper by *P. J. Garrat* and *K. A. Knapp.* A solution of *(1)* in THF is converted, by treatment with *n*-butyllithium in hexane at room temperature *in vacuo,* into a deep red solution whose NMR spectrum indicates the presence of the non-planar, non-aromatic anion *(2).* Addition of water regenerates *(1).* When



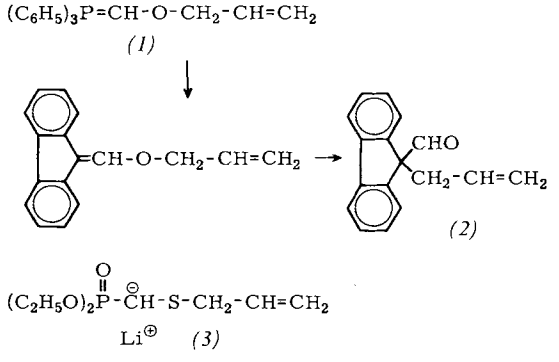
the solution of *(2)* is left to stand it forms the planar, aromatic anion *(3)* (detected by NMR spectroscopy), which yields *(4)* on treatment with water. Assuming the conversion of *(2)* into *(3)* to be a first order reaction, ΔF is 8.9 kcal/mole between 30 and 52° C and K (30° C) is 7.6×10^{-5} s. ΔF affords a measure of the lower limit of the delocalization energy of *(3).* / Chem. Commun. *1970,* 1215/-Kr.

[Rd 268 IE]

The ESR spectrum of di-*tert*-butyl nitroxide in water – lipid emulsions (coconut oil) has been investigated by *B. L. Bales* and *M. E. Baur*. Distinctly different resonances for the radical in water or lipid environment were found. Intensities of the corresponding spectral lines were used to determine the partition coefficient of the radical between aqueous and lipid phases. The partition coefficient is not constant at high lipid concentration; this can be explained by a perturbation of water structure near the oil droplets. The aim of this model investigation was to study the possibility of incorporating a "spin label" into biological structures and receiving information about the properties of the environment by analysis of the ESR spectrum of the label (anisotropy, line broadening). / Chem. Phys. Lett. *7*, 341 (1970)

[Rd 270 IE]

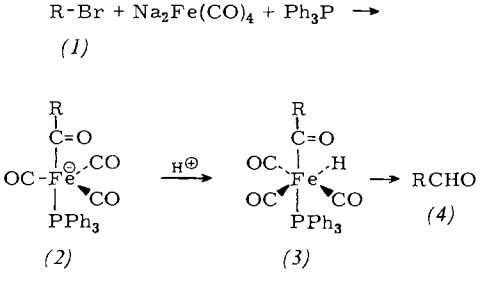
α-Allylcarbaldehydes have been obtained in two ways from ketones by *E. J. Corey* and *J. I. Shulman*. The ylide *(1)* prepared from allyloxymethylphosphonium chloride reacts with aromatic aldehydes and ketones, *e. g.* fluorenone, to give an enol ether which on thermolysis affords the α-allylcarbaldehyde *(2)*. Re-



action with the lithium salt *(3)*, which can be obtained from diethyl allylthiomethylphosphonate, is suitable for alicyclic and enolizable ketones. The allyl vinyl sulfide thus obtained is converted on thermolysis in the presence of red mercuric oxide into the α-allylcarbaldehyde. / J. Amer. Chem. Soc. *92*, 5522 (1970) / –Kr.

[Rd 273 IE]

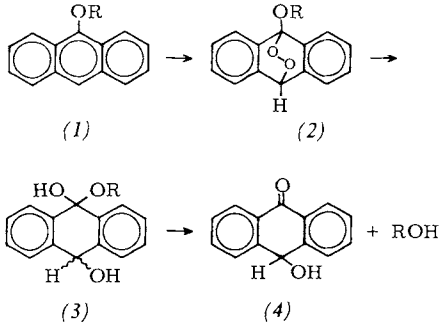
Conversion of alkyl bromides into aldehydes by reaction with disodium tetracarbonylferrate(–II), which can be prepared from sodium amalgam and pentacarbonyliron in THF, is the subject of a report by *M. P. Cooke, Jr.* Addition of triphenylphosphine renders the reagent ready for use. After addition



of the alkyl bromide *(1)* the mixture is stirred for a few hours and then treated with glacial acetic acid. It is suggested that *inter alia* the intermediates *(2)* and *(3)* are formed in the reaction leading to the aldehydes *(4)* containing one more C-atom. Examples: *(4)*. R = *n*-C_9H_{19} (yield 91 %); $C_6H_5(CH_2)_2$ (86%); $(CH_3)_2C{=}CH(CH_2)_2$ (81%); *n*-C_6H_{13}-$CH(CH_3)$ (50%). / J. Amer. Chem. Soc. *92*, 6080 (1970) / –Ee.

[Rd 274 IE]

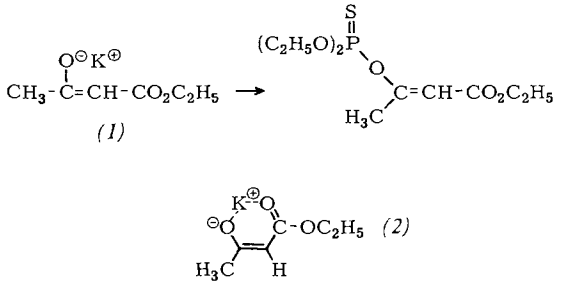
The 9-anthroxy group is suitable for the protection of hydroxy functions according to *W. E. Barnett* and *L. L. Needham*. For introduction of the protecting group the alcohol is first converted into its tosylate which then reacts with the 9-anthrolate ion to give the ether *(1)*. The cleavage involves singlet-oxygen



oxidation of the ether *(1)* at –30 °C to give the peroxide *(2)* followed by mild catalytic reduction of the O–O bond. The initial reduction product is presumably a hemiacetal *(3)* which spontaneously decomposes to 10-hydroxyanthrone and the alcohol that was protected (*e.g.* hexadecanol). / Chem. Commun. *1970*, 1383 / –Ma.

[Rd 276 IE]

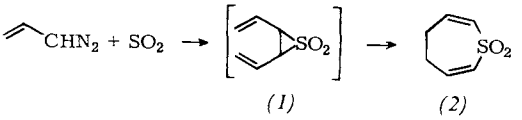
The structures of carbanions and factors determining the geometries of reactions of enolate anions have been investigated by *B. Miller, H. Margulies, T. Drabb, Jr.*, and *R. Wayne*. For example, *O*-phosphorylation of the potassium enolate *(1)* gave predominantly *cis*-isomers from reaction in non-polar solvents



and predominantly *trans*-isomers from reaction in polar solvents (in benzene: *cis/trans* = 40:1, in DMSO: 1:9). The authors present evidence that formation of the *cis*-isomers proceeds *via* chelate intermediates such as *(2)*, while formation of *trans*-isomers is due to reaction of "free" anions in which the normal repulsions between the polar groups is the geometry-deciding factor. / Tetrahedron Lett. *1970*, 3801, 3805 / –Kr.

[Rd 272 IE]

4,5-Dihydrothiepin 1,1-dioxide *(2)* has been prepared by *W. L. Mock* from 3-diazopropene and sulfur dioxide. Compound *(2)*, m. p. 111.5–112.5 °C, is possibly formed *via* the *cis*-divinylthiirane1,1-dioxide *(1)*, which subsequently undergoes a Cope rear-



rangement. On refluxing in benzene/triethylamine, compound *(2)* isomerizes quantitatively to 2,7-dihydrothiepin 1,1-dioxide. / Chem. Commun. *1970*, 1254 / –Ee

[Rd 271 IE]

Gas contents of salts from the Upper Permian formation (Germany) are reported by *H. D. Freyer* and *K. Wagener*. Samples of sylvinite, halite, and kieserite were investigated; their total gas contents are in the order of 10^{-3} cm^3 NTP/g. By comparison of different methods of disaggregation (grinding, dissolution, melting) of samples it can be concluded that the gases are molecularly dispersed in the lattice. Probably they were in equilibrium with the components of the solution when the salt was deposited. Consequently, gas analyses can supply information about the atmospheric composition at the time of salt formation. Mass spectrometric gas analyses are reported of N_2, O_2, Ar, CO_2, CH_4, H_2, and sometimes, H_2S./Z. Naturforsch. *25a*, 1427 (1970) / –Hz [Rd 269 IE]

BOOK REVIEWS

Catalysis by Nonmetals. Rules for Catalyst Selection. By *O. V. Krylov.* In the series: Physical Chemistry. A Series of Monographs. Academic Press, New York-London 1970. 1st Edit., x, 283 pp., $ 14.00.

This book is an English translation of the well-known Russian author's work. It deals with the catalytic properties of oxides, sulfides, solids with acid or basic surface groups, and other one-component nonmetals. Thus, at first glance the book can be seen to be the counterpart of the widely read monograph by *G. C. Bond* "Catalysis by Metals" which was published by Academic Press in 1962. The main object of *Krylov*'s work is to give rules for the choice of catalysts for certain reactions such as oxidations, hydrogenations, dehydrogenations, hydrations, dehydrations, exchange and decomposition reactions, isomerizations, cracking, alkylations, and polymerizations.

The book is divided into two sections, the first of which is reserved for a description of the correlations between the catalytic activity of solids – selectivity is unfortunately not considered – and their physico-chemical properties (for example, type of conduction, charge-carrier concentration, doping, width of the forbidden zone, electron work function, ionic radius and valence, electronegativity of the atoms, acidic or basic surface groups, dielectric constant, crystal type, and lattice constant). In this connection, due attention has also been given to theoretical discussions of reaction mechanisms. The second part of the book summarizes and describes the reactions for which catalysts can be found by applying the principles discussed. Finally, an appendix summarizes the major physicochemical parameters of a large number of solids. The list of references extends essentially as far as 1964.

The book will appeal primarily to physical chemists engaged in catalyst research and development.

Ernst-Günther Schlo [NB 918 IE]

Modern Reactions in Organic Synthesis. Edited by *C. J. Timmons.* Van Nostrand-Reinhold Company, London 1970. 1st Edit., vi, 311 pp., numerous formulas, bound £ 5.10.

The title of this book is too ambitious. The editor himself states in the foreword: "This book reviews, within chosen fields some of the synthetic methods recently developed or applied that seem important in the views of the contributors."

In seven chapters the book's eight authors discuss the following topics: reduction and oxidation methods; the use of free radicals in syntheses; electrochemical and photochemical methods; and the synthesis of aromatic and heterocyclic compounds. The references cited cover the period from 1960 to 1967/68. One wonders why the book has only just been published since, in spite of the lavish use of structural formulas, its careful preparation, and the detailed index, it should not have taken so much time to produce.

The individual chapters contain many relevant references (more than 1100 in all). However, in the case of oxidations with ozone, for example, no mention is made of the useful tetracyanoethylene variant [Chem. Ber. *96*, 1564 (1963)] and, in the case of the acyloin reaction in the section on radicals, there ist no reference to the valuable modified method in the presence of trimethylchlorosilane [Chem. Ber. *100*, 3820 (1967); Tetrahedron Lett. *1968*, 586].

The book should be kept in libraries for students in the final stages of their degree courses but it is of limited value to teachers and research workers.

Dieter Seebach [NB 919 IE]

The Radiation-Induced Decomposition of Inorganic Molecular Ions. By *E. R. Johnson,* Gordon and Breach, New York-London-Paris. 1970. 1st Edit., ix, 144 pp., Bound £ 18.–.

Comprehensive monographs on specialized topics from the large field of radiation chemistry have long been appearing in the English-speaking world. Thus, the present book, which attempts to give a comprehensive survey of the action of high-energy radiation on inorganic crystalline solids, is aimed at the specialist. Basic concepts of radiation chemistry are mentioned in a few introductory sentences. Somewhat more space is devoted to necessary information on solid-state physics (natural defects) and crystal-lattice defects caused by high-energy radiation. After a short description of the crystal properties that change under the effect of radiation and of the factors that cause these changes, three-quarters of the book is devoted to the results of the radiation-induced decomposition of inorganic salts (nitrates, chlorates, perchlorates, bromates, azides, sulfates, carbonates, and permanganates). Attention is also paid to the radiolysis products with their G values, the electronic absorption spectra, and the ESR spectra of the irradiated crystals.

In the case of the more thoroughly investigated nitrates, chlorates, bromates, and perchlorates, the kinetics and mechanisms of radiation-induced decompositions are discussed. A critical appraisal of the results, some of which are controversial, is given at the end of every relevant chapter.

Typically, only three of the 182 references (ranging up to 1968/9) cited in this successful book come from German journals. This cannot be dismissed with the usual explanation, namely that Americans read only English literature, since Russian journals, for example, are often quoted.

Hans Güsten [NB 921 IE]

Mensch und Arbeit im Chemiebetrieb (Man and Work in the Chemical Industry). General editor *W. Schneider.* Verlag Mensch und Arbeit, Munich, 1970. 1st Edit., 10 pp., ring binder, DM 16.80.

Society has changed considerably in the course of this century, not least in the sphere of working life. An employee in industry can no longer be regarded as a mere subordinate or as mere work power – he is developing more and more into an actively participating individual. Comprehensive professional training and further education are constantly improving the employee's ability to understand his sphere of work and to act fruitfully

on his own initiative. The employee is increasingly assuming the character of a coworker.

This change means that a new style of management is needed in industry and that, in particular, the old authoritarian principles must be abandoned. Many employers have already come round to this new way of thinking, often by force of circumstances.

The working group of the industrialists associations of the German chemical industry has for many years been attempting, by suitable training at middle management level, to take account of the changing circumstances. In this connection it has been running, among other things, business management courses and seminars for young graduates at Rech an der Ahr. This group also regularly produces two publications: "Informationsbrief für Führungskräfte in der Chemischen Industrie" (Information Sheet for Management Personnel in the Chemical Industry) and "Blätter für Vorgesetzte" (Notes for Managers).

The working group has now further supplemented its efforts in this field with the publication of the manual "Mensch und Arbeit im Chemiebetrieb". This appeared for the first time in 1966 as a pocket book under the title of "Mensch und Arbeit" (Man and Work) and, with more than 20000 copies, it has proved its worth as an organ of information for employers and as a reference book for everyday work in industry.

In separate chapters this manual deals with a very wide variety of practical problems, giving explanations, hints, and guidelines. A wide range of problems, which it would take too long to enumerate in full, are broached: design of the working area and its surroundings, wages systems, average productivity as a function of working time, question of health and safety, the management of men, information, assessment of staff, grading according to performance, training, fundamentals of industrial law and regulations, and information on the chemical industry. Many sections are supplemented and clarified with tables and statistics. It is obvious that trouble has been taken to provide employers with a compendium of relevant information which should make their work easier. It is openly admitted that there is no universal formula for solving managers' problems or for evolving management methods. Thus the book is made up in the form of a file in which the individual "chapters" are arranged as separate entities. By changing old material or adding new the manual can easily be kept up to date. It will best fulfil its task of giving advice and help to the reader if, as recommended in the introduction, it is not put into a bookcase but is left instead on the desk or workbench; if this is done, "it will certainly not be long before you find cause to use it". If such frequent use is made of it, its value will soon become obvious to the reader.

Hermann Reis [NB 922 IE]

Albert Einstein/Arnold Sommerfeld: Briefwechsel. (Exchange of Letters between Albert Einstein and Arnold Sommerfeld.) Ed. and annotated by *A. Hermann.* Schwabe & Co., Basel-Stuttgart 1968. 126pp., linen DM 18.80.

The editor describes this outwardly modest collection as "sixty letters from the Golden Age of modern physics". It provides what is probably the most stimulating reading in this field. Cleverly and skilfully annotated, these letters give a unusually vivid impression not only of the personalities of these two great physicists and of the intellectual conflict behind their achievements but also of the times – fickle and finally disastrous – which (by chance?) gave a home to these achievements. It is moving to see how personal quarrels arising from external or internal misunderstandings stand in stark contrast with scientific and theoretical discussions which time and again bridge the gap between these two men whose thoughts and feelings are in many respects so different.

One does not need to be interested in the history of physics to derive pleasure from this volume. The letters will be richly rewarding if one merely recalls that even the highest scientific achievements are the achievements of a human being.

Helmut Grünewald [NB 915 IE]

Handbook of Chemistry and Physics. Ed. by *R. C. Weast* and *S. M. Selby.* The Chemical Rubber Co., Cleveland 1970. 51st Edit., 2423 pp., bound DM 99.80.

After celebrating its jubilee, the fiftieth edition in 56 years, this great handbook has now appeared in a new edition for the 51st time. When it was first published people were acquainted with electrons, protons, and neutrons but knew practically nothing about them. Today the book has seven pages on these three elementary particles alone. Similar is the situation with chemical bonding (now twelve pages with data on bonding forces) and with superconductivity (fourteen pages of tables).

The size of the book, which increases with each edition, gives cause for concern. It now contains 2423 pages, 2100 of which (*i.e.* 87% of the whole book) are given over to tables which are important for the chemist. It must be said, however, that the editors know how to make the user very quickly forget the size of the book by their excellent arrangement and layout.

As always, numerous tables in this edition have been supplemented and brought right up to date. As always, too, a strip of gold foil is supplied with the book. Its purpose? On the cover there is a blank, deep red area, which is offset against the surrounding blue by a broad gold border, where one can put one's initials – in 23 carat gold. Not an everyday opportunity, but one which is thoroughly in keeping with the value of the work.

Helmut Grünewald 916 IE]

Taschenbuch für Chemiker und Physiker (Handbook for Chemists and Physicists). Ed. by *K. Schäffer* and *C. Synowietz.* Vol. III: Properties of Atoms and Molecules. Springer-Verlag, Berlin-Heidelberg-New York 1970. 3rd Edit., viii, 670pp., 112 figures, bound DM 48.–

This volume contains data on the physics and chemistry of atoms and molecules. Six sections give a survey of atomic nuclei, their most important properties and reactions, information on atomic and molecular spectra and the data that can be obtained from them, and tables of ionic radii, ionization potentials, effective cross sections, polarizabilities, and dipole moments. The relationships between molecular and directly observable macroscopic properties are also dealt with, and finally there is a table of spectral lines. Most tables are introduced by basic textual material which serves not only to clarify the tables but also to give a brief recapitulation of the most important relevant theoretical points. These introductions make the book more than a mere compendium of tables. They skilfully give the reader the help he needs to find his way through the wealth of data.

The arrangement of the tables, the dimensional data, and the explanation of the abbreviations and symbols are exemplary. Only the formulas occasionally leave something to be desired (dots instead of dashes). One cannot check at a desk the accuracy of the immense amount of data given in a handbook. One can only hope that such a book has as many readers as it deserves, so that the editors are rewarded for the enormous amount of work the have put into it.

Helmut Grünewald [NB 917 IE]

Biochemistry. The Molecular Basis of Cell Structure and Function. By *A. L. Lehninger.* Worth Publ. Inc., New York 1970. 1st Edit., xii, 833pp. with numerous figures, bound, *ca.* DM 65.–.

There is no lack of good American textbooks on biochemistry, but the present book by *A. L. Lehninger,* well known for his descriptive powers, will occupy a special place among them. It is not a summary of the structure and metabolism of biologically important compounds, nor is it built up simply on ideas about the dynamics of all molecules; instead, it is based on the concept that the conformity of molecular interactions with physical and chemical laws forms the basis of structure and function, and on the "molecular logic of living organisms". The cell forms

an open self-reproducing system consisting of numerous consecutive and interconnected chemical reactions catalyzed by organic molecules present in the cell.

Logically, the book begins with the various classes of biological molecules and their physicochemical behaviors, the principles of separation and analysis procedures being discussed wherever relevant. The author then moves on to an analysis of enzyme reactions, their arrangement into reaction chains and metabolic cycles, and the regulatory mechanisms within the cellular environment. He next deals with the flow of substances and particles through the channels of this machinery and with the question of how chemical energy becomes free and available in the form of ATP, enabling the occurrence of the energy-consuming reactions and physiological work of the cells, like movement, replication, and differentiation, with their complexity and high degree of organization. In this way the reader never sees the substances in isolation but alway as parts of a complete interacting system. The picture is admirably completed with a consideration of the origin and evolution of life.

The above patterns of thought and the extensive knowledge and teaching experience of the author combine to make this book unusually stimulating. The style is often rather stilted and apodictic but this does not detract from the work's excellent coverage of the topic and its didactic and esthetic qualities: figures, schemes, and underlinings break up the subject matter, clarifying it and making it easy to remember; the clear print and good layout make it a dependable and practical textbook.

Apart from the nowadays obligatory references (what student has ever used them?), each chapter contains a short summary of the subject matter, problems, and exercises. These are sometimes rather difficult, particularly since they are often not very clearly formulated. The appendix with the solutions, however, makes it possible to work them backwards. The interlinking of the chapters by cross references often leaves something to be desired, and a few cases of didactic license are superfluous. However, these are mere trifles compared with the overall impression of a thoroughly successful piece of work. It is a book which, both from the point of view of composition and layout, one would have liked to have had in one's own student days, or to have written oneself. All universities where students of medicine and biology receive a thorough training ought to have copies in their libraries.

L. Jaenicke [NB 925 IE]

Adsorption. Introduction to Physisorption and Chemisorption. By *G. Wedler*. Volume 9 of "Chemische Taschenbücher", edited by *W. Foerst* and *H. Grünewald*. Verlag Chemie, Weinheim/Bergstr. 1970. 1st Edit., vii, 224 pp., 75 figures, 9 tables, paperback, DM 24.–.

This book, which is described as an introduction to adsorption, is intended less to give a theoretical and systematic survey of this field than to provide an experimentally oriented description of phenomena that occur during adsorption of gases on solid surfaces. Arranged according to methods of investigation, the book describes the effects occurring both in the adsorbent and in the adsorbate during adsorption and their measurement. Well-chosen examples of applications of these measurement techniques are used to show what information can be obtained from such investigations, and numerous references are given.

Since the majority of the methods discussed are "modern" techniques of surface investigation, this work constitutes a valuable addition to the existing textbooks dealing with this subject. However, there is no mention of methods like Auger spectroscopy and ellipsometry, and one wonders whether the author should not have striven for completeness of the experimental methods discussed to comply with the aim of the series "Chemische Taschenbücher", namely to supplement and enlarge upon the material contained in the basic textbooks.

K. H. Beckmann [NB 927 IE]

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Blood Coagulation and Fibrinolysis

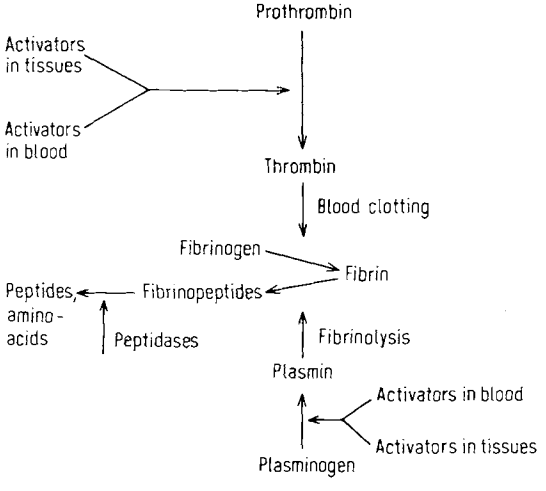
Norbert Heimburger and Heiner Trobisch[*]

As a result of advances in protein chemistry it is now widely accepted that blood coagulation proceeds via a series of reaction steps of the nature of enzyme-substrate reactions catalyzed by phospholipids. This also applies to the compensatory process of fibrinolysis. The factors taking part in both mechanisms as well as the inhibitors regulating the equilibrium have been shown to be proteins, some of them with a high carbohydrate content. Modern diagnostic methods and therapy are based on this knowledge.

1. Introduction

One of the most important physiological properties of blood is its ability to coagulate, and even to become completely solid and liquid in turn. In principle, both phenomena are manifestations of enzymatic reactions of a plasma protein, fibrinogen. The conversion of the soluble fibrinogen, present at a concentration of 0.2–0.4% in human plasma, into an insoluble, easily polymerizable derivative, fibrin, characterizes the process of blood clotting, while dissolution of the crosslinked fibrin marks the process of fibrinolysis. Coagulation and fibrinolysis succeed each other under physiological conditions. Such interplay guarantees that fibrin is produced when required for hemostasis and is degraded when it has fulfilled its biological function after the wound has healed. Hence, fibrinolysis can be considered as a further stage in the coagulation of blood.

Coagulation and fibrinolysis are under enzymic control. Thus thrombin catalyzes the change of fibrinogen into fibrin and plasmin the hydrolysis of fibrin. Both enzymes, which are endopeptidases, possess no strict substrate specificity. The body is protected by a safety measure ensuring that under physiological conditions these enzymes circulate in the blood not in their activated form but as proenzymes. The activation of the proenzymes is also under enzymatic control. Thus some enzyme activators must first be generated from their precursors present in the blood. The factors required are often separated from the bloodstream by a cell or tissue barrier, which may also hold the activators back. Such an arrangement ensures that they are formed and released only when tissues are damaged or the surface of cells and especially of blood vessels is altered. This sequence of events guarantees that thrombin and plasmin are generated only locally and only in response to a real physiological need.



Scheme 1. Blood coagulation and fibrinolysis.

The reactions participating in blood clotting and fibrinolysis are very similar, although they exert opposite effects (Scheme 1). In each process the biological activity is associated with a proteolytic enzyme, thrombin or plasmin, which exists as inactive proenzyme in the blood and is activated by activators localized both in blood and in

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tissues. In a healthy organism clotting and fibrinolysis are in dynamic equilibrium. If the enzyme reactions overshoot in one or the other direction, the results may be fatal. Hemorrhage, thrombosis, and vascular disease can be the biological consequences, and arteriosclerosis may also ensue from a disturbance of this dynamic equilibrium[1].

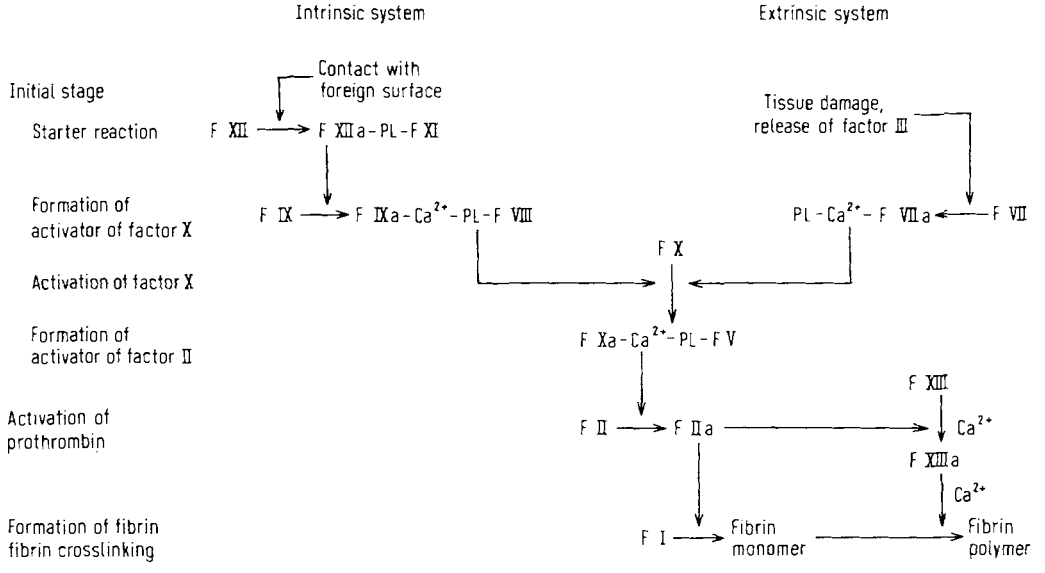
Disturbances of the hemostatic equilibrium can nowadays be diagnosed and treated appropriately thanks to the knowledge gained from research on blood clotting. This means that the factors that determine the state of the coagulation and fibrinolysis system are known and can be measured.

2. Blood Clotting

As many as twelve factors present in the plasma and additional components derived from thrombocytes and cells are involved in the process of coagulation, which extends over several reaction steps. The plasma factors are predominantly proteins, some of which have enzymatic properties and which circulate in the form of inactive precursors in the blood; they can be characterized by techniques customary in protein chemistry, but only a few have so far been isolated in pure and biologically active states. The cellular factors active in the clotting process are phospholipids, a class of substances widely distributed as components of cell membranes. These lipids have been shown to catalyze important steps of enzyme activation during the process of clotting. This fact could explain why cellular disintegration inevitably leads to hypercoagulability.

The process of blood clotting can be initiated along two different pathways, both of which lead to the activation of factor X and hence to the formation of the prothrombin activator[7,8] (Scheme 2). The site of the stimulus governs the sequence of reaction steps, which lie either on an extrinsic[2] or an intrinsic[3] pathway. The intrinsic system is the more complicated; it involves several reaction steps, and since it incorporates several safety measures it tends to be relatively sluggish. In contrast, the extrinsic system reacts spontaneously. It can maintain the blood volume constant in an emergency, thus fulfilling what is probably its most important function. Platelets and vessels mutually assist the blood clotting system: a traumatic stimulus produces arterial contraction; an annular layer of muscle in the arterial wall regulates vascular tone; vaso-active peptides and biogenic amines affect muscular tension. These pharmacological substances, either vasoconstrictors or vasodilators, are produced by a kind of side reaction during coagulation and fibrinolysis.

A damaged vessel whose surface is foreign to the blood activates the intrinsic clotting mechanism. This applies, in particular, to collagen, which forms the supporting matrix of blood vessels, for blood platelets adhere to the collagen fibers, form aggregates on the unphysiological surface, and fuse into a viscous, white plug that effects a preliminary, mechanical closure of the wound[4,5]. The thrombocytes release their ADP which acts directly on the platelet membranes and catalyzes aggregation[6].



Scheme 2. Clotting mechanism (schematic; see also Table 1). PL = phospholipid.

During this viscous metamorphosis intracellular coagulant substances are released among which platelet factor 3, a phospholipid, and antiheparin, platelet factor 4, are the most important[6].

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[2] *W. Staub* and *F. Duckert*, Thrombos. Diathes. Haemorrh. *5*, 402 (1961).

[3] *G. H. Müller*, Thrombos. Diathes. Haemorrh. *14*, 417 (1965).

[4] *S. Karpatkin* and *R. M. Langer*, J. Clin. Invest. *47*, 2158 (1968).

[5] *M. Corn*, Nature *212*, 508 (1966).

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Table 1. Factors participating in the clotting process. They have been numbered with Roman numerals in the order of their discovery by a decision of the International Committee on Nomenclature. F IV is Ca^{2+}, F VI is not an independent factor but is probably identical with F V. Activated factors indicated by "a".

Factor	Synonyms	Source of preparation	Electrophoretic mobility/ Molecular weight	Function and special properties	Plasma concentration	Site of formation
I	Fibrinogen	Human plasma	β_2-Globulin 360000 (φpeak)	β_2-Glycoprotein, split by F IIa at two specific arginyl sequences to give fibrin monomers	200-400 mg/ 100 ml	Liver
II	Prothrombin	Human plasma	α_2-Globulin 52000	Proesterase activated by F Xa to an endopeptidase which is relatively fibrinogen-specific [32]	10-15 mg/ 100 ml	Liver, dependent on vitamin K [35, 36]
IIa	Thrombin		34000 [55]			
III	Thromboplastin, thrombokinase	Human and animal organs, preferably lung and brain.	Up to 3×10^6	Tissue factor, released on injury together with phospholipids [29, 30]	Normally not present in plasma	Cells
IV				Ca^{2+}		
V	Accelerin, accelerator globulin, labile factor	Bovine plasma [54]	β-Globulin Unknown	Very sensitive protein, stabilized by Ca^{2+}. Catalyzes in conjunction with phospholipids and Ca^{2+} the activation of prothrombin by F Xa [42, 43, 54]	Unknown	Liver?
VII	Proconvertin	Bovine plasma [31]	β-Globulin [31] 63000	Proenzyme, activation by contact with cell fragments; cofactor of F III to form activator of F X [31]	Unknown	Liver, dependent on vitamin K [31]
VIIa	Convertin		48000 [31]			
VIII	Antihemophilic globulin A, antihemophilic factor	Human, bovine, porcine, and rabbit plasma	β_2-Globulin [23] Unknown	No proof of enzyme character, stabilized by Ca^{2+}, substrate of F IXa [24]	Unknown	Spleen, RES [a]
IX	Christmas factor, antihemophilic globulin B	Human and bovine plasma	β_2-Globulin Unknown		Unknown	Liver, dependent on vitamin K
IXa			Unknown	Present in a complex with F VIII, Ca^{2+}, and phospholipids to form activator of F X [21]		
X	Stuart-Prower factor	Bovine plasma [32]	α_1-Globulin 50000	Proesterase, converted by endogenously or exogenously formed activators to arginine esterase [9, 32]	10 mg/100 ml	Liver, dependent on vitamin K
Xa			34000 [32]			
XI	Plasma thromboplastin antecedent	Not yet isolated	β_2-Globulin Unknown	Substrate of F XIIa; both form a complex with phospholipids catalyzing activation of F IX	Unknown	RES? [a]
XII	Hageman factor, contact factor [13, 14]	Bovine plasma [16]	β_2-Globulin [16]	Proesterase, activation on foreign surfaces to give arginine esterase (F XIIa) [16]	1 mg/100 ml [15]	RES? [a]
XIIa			*ca.* 240000 [14-16]			
XIII	Fibrin stabilizing factor, fibrinase	Human plasma	β_2-Globulin 290000	Transglutaminase, activated by thrombin; links fibrin monomers through peptide bonds into a firm network	1-2 mg/100 ml	Liver
XIIIa	Plasma transglutaminase					

[a] RES = reticuloendothelial system.

Table 1 lists the factors involved in the process of coagulation, showing their most important properties. Several of the factors are enzymes. Thrombin (F IIa) and the activated factors X and XII (Xa and XIIa) are esterases, and factor XIII is a transamidase in its activated form (XIIIa)[8]. The biochemical nature of most of the factors has not yet been clarified. There are indications that factors II, VII, IX, and X are related to one another. According to *Seegers*[9], they do not exist as individual proteins but are dissociation and association products of prothrombin (F II). Since clotting factors are particularly labile this question has not yet been finally answered; even the most modern techniques do not prevent denaturation and inactivation. The function of coagulant proteins naturally requires that they should be highly sensitive (see Section 2.1.1).

2.1. The Intrinsic Pathway

2.1.1. Initial Stage

In the starter reaction contact of blood with nonphysiological surfaces, such as skin, cellular debris, collagen fibers, and arteriosclerotic layers initiates the clotting process. At the same time, the Hageman factor (F XII), a proesterase, is changed into an active arginine esterase[10–17]. Other proteins acting as protective colloids pre-

[7] *F. Jobin* and *M. P. Esnouf*, Biochem. J. *102*, 666 (1967).

[8] *W. H. Seegers*, Annu. Rev. Physiol. *31*, 269 (1969).

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[10] *O. D. Ratnoff* in *E. B. Brown* and *C. V. Moore:* Progress in Hematology. Grune and Stratton, New York 1966, p. 204.

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vent an accidental activation of the Hageman factor in the blood. The technique used for enrichment and isolation makes use of the high affinity of the proenzyme for foreign surfaces[17]; however, the activated Hageman factor (F XIIa) obtained in this way is not stable indefinitely[18]. That is probably why the physicochemical properties of the Hageman factor are not yet fully known. A deficiency of factor XII does not apparently constitute a hemorrhagic disease, as may be seen from the clinical history of the first patient, by name of *Hageman*, with a hereditary deficiency of factor XII[22]. However, if factor XII is activated inside the body disseminated intravascular coagulation will occur, with fatal results. Since the Hageman factor also catalyzes the conversion of kallikreinogen into kallikrein, the kallikrein-kinin system (and indirectly also fibrinolysis) is activated at the same time as the intrinsic clotting mechanism[19, 20] (Scheme 4).

Factor XII once activated (F XIIa) forms an enzyme-substrate complex with factor XI in the presence of phospholipids; the starter reaction consists essentially in the formation of this complex, which then catalyzes the activation of factor IX, the most important component of the intrinsic system activating factor X[21].

The chemistry of factor XI is almost unknown: it has hitherto defied all attempts at isolation. However, its existence is demonstrated by a rare hereditary hemorrhagic disease caused by its deficiency in or absence from the blood.

When factor IX in its activated form (IXa) combines with another plasma protein, factor VIII, and with phospholipids in the presence of calcium ions, the complex thus formed constitutes the activator of factor X. No conclusive proof for this enzymatic step has yet been obtained because factor IX has not hitherto been isolated or characterized in any way.

Factor IX appears to possess neither protease nor esterase properties, because its action is not affected by diisopropyl fluorophosphonate to which esterases having serine in the active site are sensitive. Calcium ions catalyze the activation of factor IX, heparin blocks it. The synthesis of factor IX which takes place in the liver is dependent on vitamin K. A deficiency of factor IX which is inherited is responsible for hemophilia B, the second most frequent hemorrhagic disease.

Factor VIII, antihemophilic globulin A (AHG–A), is one of the best known clotting factors. Its inherited absence or deficiency is the cause of the most frequent familial hemorrhagic disease, *i.e.*, hemophilia A. The term "antihemophilic globulin A" derives from the fact that its administration represents the only effective treatment of hemophilia A. This globulin, which is probably synthesized in the spleen, belongs to the group of β_2-globulins of the plasma and has a relatively high molecular weight[23, 24].

It has not been possible to prepare AHG–A in a pure state, because it is very labile. Chelating agents inactivate it irreversibly by removing calcium ions which may stabilize AHG–A; alternatively, factor VIII may be a complex made up of several individual proteins or subunits. Neither theory has yet been proved. The most useful procedure for preparing therapeutically active concentrates is also the simplest, *i.e.* cryoprecipitation, where use is made of the differential solubilities of plasma proteins on freezing and thawing.

Activation of factor X is the first step in the cascade-like sequence of reactions common to the intrinsic and extrinsic mechanism of clotting and yet catalyzed by activators of different composition (Scheme 2). Enzymes catalyze the transformation of factor X to yield an arginine esterasé (F Xa) with a high affinity for calcium ions[28], which is evidently an important prerequisite for the formation of the prothrombin activator from factor Xa, calcium ions, phospholipids, and plasma factor V.

The intrinsic and extrinsic mechanisms converge at the point where the prothrombin activator is formed; details will therefore be discussed in the appropriate Section in order to facilitate an understanding of the subsequent activation of prothrombin.

2.2. The Extrinsic System

2.2.1. Initial Stage

When a wound is inflicted, blood will rush out of the injured capillary vessels into the surrounding tissue. Simultaneously substances differing in chemical nature and capable of promoting blood coagulation will be washed out of the damaged cells. Such substances are often still bound to cellular components; they are present in particularly large amounts in microsomes. This fraction of cell particles is called tissue thromboplastin or factor III[29, 30]; its release may be regarded as the starter reaction.

The interaction between tissue factor III and a plasma cofactor (F VII, proconvertin), which is carried by the blood to the wound, is the next step in the formation of the activator of factor X. The activation of factor VII to give F VIIa, which occurs on contact with factor III, is accompanied by a reduction of the molecular

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[30] *A. D. Bangham,* Nature *174,* 791 (1954).

[31] *H. Prydz,* Scand. J. Clin. Lab. Invest. *17,* Suppl. 84, 78 (1965).

weight[31], as investigations on isolated factors obtained from bovine plasma and serum have shown[31]. The difference in the molecular weights between the inactive and activated forms of F VII may indicate that activation is enzymatic, but no experimental evidence has yet been obtained[33,34].

An enzyme, factor Xa, arising on activation of factor X catalyzes the hydrolysis of *N*-substituted arginine esters[25-27]. It is liberated from the proesterase enzymatically; the reaction is catalyzed by trypsin or Russel viper venom *in vitro*. The activators formed either endogenously or exogenously catalyze this activation in a comparable manner *in vivo*[9].

Factor X was prepared in high purity for the first time from bovine plasma[32]. The isolation is carried out by adsorption onto $BaSO_4$ or $Ca_3(PO_4)_2$, fractional elution from these adsorbents, chromatography of the eluates on cellulose ion exchangers, and final separation on a molecular sieve. A uniform preparation is obtained under these conditions only if diisopropyl fluorophosphonate is added to the buffers[32]; this inhibitor prevents an enzymatic degradation and inactivation during the isolation. The molecular weight is decreased and the electrophoretic mobility altered as a result of activation[32]. Factor Xa is the enzymatic and also the most important component of the prothrombin activator complex.

The prothrombin activator catalyzes the transformation of prothrombin (F II) to thrombin (F IIa). Several components of the prothrombin activator take part in the reaction: factor Xa and factor V, which is a plasma globulin of uncertain nature, phospholipids, and calcium ions. The phospholipids provide the reaction surface on which the enzymatic conversion of prothrombin by factor Xa takes place. Since factor V determines the reaction rate, it is referred to as accelerator globulin. It is assumed that factors V and Xa are held inside the lipid micelles in such a way that both come into close contact with the prothrombin molecule[42-44], thus satisfying an essential condition for activation, *i.e.* a partial hydrolysis.

2.2.2. The Activation of Prothrombin

Although prothrombin (F II) is one of the trace proteins in human plasma, its presence in plasma can be detected by modern electrophoretic techniques as well as by biological tests.

When human plasma is subjected to electrophoresis in agarose gel containing fibrinogen, a turbidity arises in the α_2-globulin region if tissue thromboplastin (F III) and calcium ions are allowed to diffuse from a slot parallel to the direction of migration. The turbidity occurs in the electrophoretic position of prothrombin where it encounters the tissue thromboplastin diffusing in, so that thrombin could be formed. The turbidity in the plate is due to the formation of fibrin. This biological test can be combined with an immunological assay using a specific antiserum against prothrombin but not a multivalent antihuman serum. The concentration of prothrombin in plasma can be determined quantitatively in this manner. It is 10–15 mg/100 ml, and thus of the same order of magnitude as that of human plasminogen[37].

The synthesis of prothrombin (F II), which depends on vitamin K, occurs in the liver together with that of factors VII, IX, and X[35,36]. The prothrombin complex thus comprises four protein factors. Serious diseases of the liver upset the synthesis of these proteins. This also applies to vitamin K deficiencies caused by partial or complete elimination of the intestinal flora, *e.g.* in diarrhea, after treatment with non-absorbable antibiotics, or in cases of obstructive jaundice when fats are not readily reabsorbed and vitamin K is not taken up at all.

The dependence of the synthesis of factors comprising the prothrombin complex on vitamin K is pharmacologically important because the dicoumarols and indandiones, being antagonists of vitamin K, can be employed successfully in the prophylaxis of thrombosis and the treatment of cardiac infarction[35,36]. Recent findings on the effects of these long-acting anticoagulants contradict the original idea of a total inhibition of synthesis. These drugs act not so much by affecting the rate of synthesis of the prothrombin complex as by inducing the formation of a biologically unusable prothrombin molecule which will react with the prothrombin activator but not give rise to any thrombin[35-38].

In principle, the same techniques are applied to the isolation of prothrombin as to the preparation of factor X. Since the two proteins have such similar properties, they can be separated only with difficulty even when using the most varied methods of fractionation. It has not been possible to obtain a uniform preparation satisfying all purity criteria of proteins, because autocatalytic inactivation cannot be prevented entirely[39-41].

Prothrombin, which has a molecular weight of 52000, breaks up during activation into at least three components, one of which is identical with thrombin (mol. wt. = 34000)[25-27].

The prothrombin activator, a complex of phospholipids with factors Xa and V and with calcium ions, catalyzes the transformation of prothrombin to thrombin; the reaction appears to be a specific proteolytic hydrolysis, which is also catalyzed by trypsin and which proceeds autocatalytically in a 25% solution of sodium citrate[9]. Factor Xa on its own catalyzes the reaction only inadequately, although it cleaves arginine esters[32]. The reaction proceeds very sluggishly in a purified system containing prothrombin, but once factor V, phospholipids, and calcium ions are added, the rate of the reaction increases 1000-fold without simultaneous enhancement of ester hydrolysis. This result shows that factor V ac-

[32] *C. M. Jackson* and *D. J. Hanahan*, Biochemistry *7*, 4492, 4506 (1968).

[33] *Y. Nemerson*, Biochemistry *5*, 601 (1966).

[34] *W. J. Williams* and *D. G. Norris*, J. Biol. Chem. *241*, 1847 (1966).

[35] *H. C. Hemker, J. Van der Meer, R. Hodge*, and *E. A. Loeliger* in *J. Van der Meer:* Pharmacological Aspects of Vitamin K1. Schattauer-Verlag, Stuttgart 1968.

[36] *E. F. Mammen*, Internist *1*, 2 (1969).

[37] *P. O. Ganrot* and *J. E. Nilehn*, Scand. J. Clin. Lab. Invest. *21*, 238 (1968).

[38] *J. E. Nilehn* and *P. O. Ganrot*, Scand. J. Clin. Lab. Invest. *22*, 17 (1968).

[39] *D. Heene* in *H. Schröer:* Biochemie und Aktivierung des Prothrombins. Schattauer-Verlag, Stuttgart 1968, p. 3.

[40] *G. F. Lanchantin* and *J. A. Friedmann*, Vox Sanguinis *9*, 228 (1964).

[41] *W. H. Seegers et al.*, Texas Rep. Biol. Med. *23*, 675 (1965).

celerates the activation of prothrombin specifically, but only in a medium containing phospholipids. For this reason it is assumed that the activation of prothrombin takes place on the surface of the lipid micelles[42–44]. Such a concept would also explain the effect of prolonged-action anticoagulants on the organism: competitive blocking of the complex of factors Xa and V and of lipid (prothrombin activator) by pathologically modified prothrombin greatly reduces the rate of reaction[35].

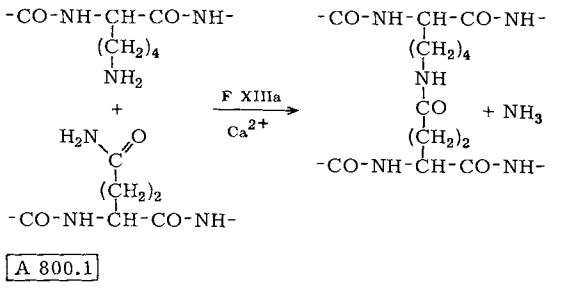
Thrombin (F IIa) is a highly specific protease whose most important function is to catalyze the coagulation of fibrinogen. However, thrombin loses this property progressively from the moment of its formation while retaining its ability to hydrolyze esters for a relatively long time[118]. An acetyl derivative of thrombin has been described which, though not catalyzing coagulation, cleaves synthetic esters as well as thrombin (thrombin-E)[45].

Prothrombin and factor X have much in common: the site of formation, the methods of isolation, and properties such as their enzymatic nature. These facts may justify the notion that factor X is a subunit of prothrombin from which it is generated together with thrombin or as a by-product, according to the prevailing conditions[9].

2.2.3. Formation and Crosslinking of Fibrin

The transformation of fibrinogen (F I) into fibrin monomers and their subsequent crosslinking mark the last stage of the clotting process. Both reactions are catalyzed by enzymes, *i.e.* thrombin (F IIa) and factor XIIIa, a transglutaminase.

First of all thrombin removes two relatively acidic peptides, referred to as fibrinopeptides A and B, from fibrinogen, thus generating fibrin monomers which in turn polymerize into long strands with the diameter of one fibrinogen molecule. Fibrin filaments are formed by lateral aggregation of double strands of fibrin polymers[46]. A freshly formed fibrin network is not held together by covalent bonds but is stabilized by hydrogen bonds and hydrophobic forces. Hence it is soluble in denaturing agents. Covalent crosslinking is effected by the plasma transglutaminase (F XIIIa) which thrombin sets free from factor XIII in the presence of calcium ions (see Scheme 2). The ε-amino groups of lysine and the γ-glutaminyl groups are then linked *via* amide bonds, mainly between the fibrin monomers of a double strand[47–49, 51] (Fig. 1).



A 800.1

Fig. 1. Reaction mechanism of plasma transglutaminase (factor XIIIa).

This covalent crosslinking completes the clotting process. Fibroblasts enter the clot, where factor XIIIa promotes their growth[50], and synthesize collagen which increasingly replaces fibrin; the latter is now no longer required and will be degraded. The healing of a wound has entered its final stage[52, 53].

3. Fibrinolysis

The fibrinolytic pathway is simpler and more comprehensible than the clotting pathway: the plasminogen activators are available directly and do not have to be first formed from a series of plasma factors with participation of cellular components. All the factors involved in fibrinolysis are proteins which can be characterized by customary methods of protein chemistry.

3.1. Human Plasminogen (Proactivator Plasminogen[*]) and Plasmin

Human plasminogen differs in one important respect from that of many animals: the action of streptokinase, a metabolite of β-hemolytic streptococci, converts it into plasmin. This interaction yields an intermediate complex which has the same biological effect as intrinsic activators (see Section 3.2). Hence we also apply the term proactivator plasminogen (PP) to human plasminogen[56].

Plasmin is the predominant protease circulating as an inactive precursor in blood. The concentration of the proenzyme is 15–20 mg/100 ml human plasma[57]. Since human plasma contains 7–8g of protein/100 ml isolation of the proenzyme therefore represents a 350-fold enrich-

[42] *P. G. Barton* and *D. J. Hanahan*, Nature *214*, 923 (1967).

[43] *P. A. Owren:* Coagulation of Blood, Investigations on a New Clotting Factor. J. Chr. Gundersen, Oslo 1947.

[44] *M. P. Esnouf* and *F. Jobin*, Biochem. J. *102*, 660 (1967).

[45] *R. H. Landaburu* and *W. H. Seegers*, Canadian J. Biochem. Physiol. *37*, 1361 (1959).

[46] *R. Gollwitzer, E. Karges, H. Hörmann*, and *K. Kühn*, Biochim. Biophys. Acta *207*, 445 (1970).

[47] *R. Kriel, A. G. Loewy, K. Dunathau*, and *H. J. Wolfinger*, J. Biol. Chem. *236*, 2625 (1961).

[48] *A. G. Loewy, S. Matacic*, and *H. J. Darnell*, Arch. Biochem. Biophys. *113*, 435 (1966).

[49] *B. Blombäck* in *W. H. Seegers:* Blood Clotting Enzymology. Academic Press, New York 1967, p. 628.

[*] We prefer this functional term because human plasminogen combines with streptokinase, a metabolite of β-hemolytic streptococci, to form activator as well as plasmin (see Section 3.2); in this respect it differs from the plasminogen of most mammals [56].

[50] *E. Beck, F. Duckert, A. Vogel*, and *M. Ernst*, Z. Zellforsch. *57*, 327 (1962).

[51] *K. Laki* and *L. Lorand*, Science *108*, 280 (1948).

[52] *F. Beck, F. Duckert*, and *M. Ernst*, Thrombos. Diathes. Haemorrh. *6*, 485 (1961).

[53] *F. Duckert*, Thrombos. Diathes. Haemorrh. Suppl. *13*, 115 (1963).

[54] *D. Papahadjopoulos, C. Hougie*, and *D. Hanahan*, Biochemistry *3*, 2 (1964).

[55] *S. Magnusson*, Arkiv Kemi *24*, 367 (1965).

[56] *N. Heimburger* and *H. G. Schwick*, Thrombos. Diathes. Haemorrh. *7*, 444 (1962).

[57] *H. G. Schwick* and *N. Heimburger*, Internat. Symposium über therapeut. u. experiment. Fibrinolyse, Ulm 1967. Schattauer-Verlag, Stuttgart 1969.

ment. Starting material for the preparation from human plasma is Cohn fraction III which is obtained by stepwise precipitation with alcohol; it may be extracted either with mineral acids[58] or with buffers containing lysine and ε-aminocaproic acid[59].

These amino acids are then also used for elution from ion exchange columns[60].

These basic amino acids, which enhance the solubility of human plasminogen but simultaneously inhibit activation, probably form salt linkages with the plasminogen molecule[56]. Use of buffers containing these amino acids in support media for electrophoresis has proved useful since many plasminogen preparations are poorly soluble under physiological conditions.

The sedimentation coefficient of highly purified human plasminogen measured in the gravitational field of the ultracentrifuge is $S_{20,w}=4.1$. A molecular weight approaching 90000 may be calculated on the basis of a diffusion coefficient of $D_{20,w} = 3.96$ and a partial specific volume of 0.72. In an electric field human plasminogen migrates uniformly, with a mobility corresponding to that of the β-globulins of human plasma. Human plasminogen is detected and estimated quantitatively in plasma by immuno-electrophoresis and by use of a univalent antiserum.

Human plasminogen migrates in several bands under the conditions of polyacrylamide gel electrophoresis, in which proteins are separated according to their charge and molecular shape and size (Fig. 5). The reason for this can be sought in the slight differences existing in the charge or in the molecular size and shape, due possibly to structural changes in the molecule induced by pH shifts. It can be shown by reaction with the activators and with homologous antisera that all the bands have the same specificity. When an unstained pherogram of human plasminogen is covered by a thin agar film, an immune precipitate is formed if the antiserum is allowed to migrate against the components that have diffused from the polyacrylamide gel into the agar. This precipitate extends over the whole region in which the bands are observed. Human plasminogen bound to serum migrates to the same electrophoretic position when this technique is applied.

Human plasminogen is composed almost entirely of amino acids[61]; it contains only 1.4% of carbohydrate. The polypeptide chain is held together by 22 disulfide bridges; its N-terminal amino acid is lysine and the C-terminal one is asparagine[63].

There are two additional terminal groups in plasmin, the activated molecule: N-terminal valine and C-terminal arginine (Fig. 2). Interestingly, the activation of human plasminogen is characterized by cleavage of an arginine-valine bond but the two resulting peptide chains separate only after one of the 22 disulfide bridges has been reduced. Obviously, large peptides are not removed on activation. However, the shape of the molecule is changed: its sedimentation coefficient increases and the coefficient of friction decreases. The changes in these physical properties and the appearance of the two additional end groups appear to be largely independent of the mode of activation. This has been demonstrated for autocatalytically activated plasmin as well as for the following activators: pig-heart activator, urokinase, streptokinase, and trypsin.

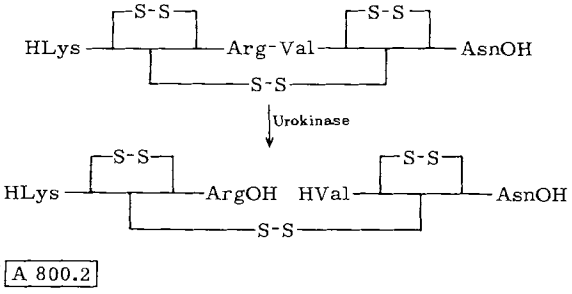


Fig. 2. Activation of plasminogen (top) by urokinase to form plasmin (bottom), schematic. Only three of the 22 disulfide bridges present are shown [63].

Since plasmin is an endopeptidase, its activity may be determined by measuring the rate of hydrolysis of fibrin, casein, or synthetic esters of lysine or arginine. However, plasmin catalyzes the hydrolysis not only of fibrin but also of other plasma proteins including certain clotting factors such as fibrinogen (Scheme 4). This reaction is of particular physiological importance because it can account for a pathological increase in fibrinolysis.

3.2. Activation of the Fibrinolytic System

The fibrinolytic system can be activated by three different mechanisms.

1) Direct conversion of the proenzyme by intrinsic activators and also by certain proteases.

2) An activator produced as an intermediate in a two-step reaction has the same biological properties as the intrinsic activators. Streptokinase is one of the relatively rare proteins having this action.

3) Some compounds of widely differing structures can have an indirect effect on the mechanism[62].

3.2.1. One-Step Activation

Natural activators are widely distributed throughout the body. As enzymes can be detected by their ability to hydrolyze synthetic esters of lysine and arginine but not high-molecular proteins such as fibrin[65]. Apart from this latter feature, their substrate specificity resembles that of trypsin which, too, is capable of activating human plasminogen in catalytic amounts. This fact is consistent with the finding that activation of the proenzyme is characterized by the hydrolysis of an arginine-valine linkage[64] (Fig. 2).

Different amounts of activator are present in various tissues[66]: Uterus, adrenals, lungs, and prostate are rich,

[58] *D. L. Kline*, J. Biol. Chem. *204*, 949 (1953).

[59] *N. Alkjaersig, P. Fletcher*, and *S. Sherry*, J. Biol. Chem. *234*, 832 (1959).

[60] *P. Wallén* and *K. Bergström*, Acta Chem. Scand. *13*, 1464 (1959).

[61] *K. C. Robbins, L. Summaria, D. Elwyn*, and *G. H. Barlow*, J. Biol. Chem. *240*, 541 (1965).

[62] *H. G. Schwick* in: Verhandl. d. Dtsch. Arbeitsgemeinsch. f. Blutgerinnungsforsch., 9. Tagung, Freiburg 1965. Schattauer-Verlag, Stuttgart 1967.

[63] *K. C. Robbins, L. Summaria, B. Hsieh*, and *I. Shah*, J. Biol. Chem. *242*, 2333 (1967).

[64] *L. Summaria, B. Hsieh*, and *K. C. Robbins:* J. Biol. Chem. *242*, 4279 (1967).

[65] *P. Kok* and *T. Astrup*, Biochemistry *8*, 79 (1969).

[66] *O. K. Albrechtsen*, Acta Endocrinol. *23*, 207 (1956).

and the testicles and spleen poor in the activator; the liver contains none at all. A high content of activator ensures that the blood maintains its fluidity. This explains why menstrual blood remains liquid or is reliquified.

Numerous problems are encountered in the isolation of pure tissue activators, because the active principle is often bound to structural elements. It can be extracted with concentrated thiocyanate solution but will reprecipitate in physiological saline. So far, two activators have been isolated from animal tissues, one from the heart muscle[67], the other from pig ovaries[65,68]; the latter has a molecular weight of 58000 and its properties as a protein and as an enzyme resemble those of urokinase obtained from human urine. Neither of the tissue activators is very soluble under physiological conditions.

Thrombocytes and erythrocytes are some of the blood corpuscles in which activators have been demonstrated; the active principle from erythrocytes, a pure erythrokinase, has already been obtained[69]. Certain body fluids and secretions are relatively rich in activators, *e. g.* urine (urokinase), amniotic fluid, and human milk, but activators are also found in lacrimatory fluid, saliva, and semen. In fact, the body makes them plentifully available wherever body fluids and secretions flow through capillaries liable to be endangered by occlusion.

One of the soluble activators is urokinase, which has been prepared in analytical purity from human urine. A volume of 2300 liters gave 29 mg of crystalline substance, the yield being 24%[70]. Urokinase, which is formed in kidney cells, has a molecular weight of 53000[71]. Like all intrinsic activators, it is an esterase that does not attack fibrin. A modified immunoelectrophoresis technique using an agar film containing fibrin as the supporting medium can demonstrate this very clearly[72]. The opalescent gel is a sensitive indicator for protease activity: clear areas appear on the agar plate wherever enzymes are located or are being generated following electrophoresis of enzyme or activator samples. Urokinase and other activators do not attack the fibrin film themselves. However, when human serum is permitted to diffuse at right angles to the migration of the activators in the fibrin film, an arc-like area of lysis is formed upon confluence as the result of proenzyme activation to plasmin. A result such as this illustrates the organization of the fibrinolytic system: neither activator nor human serum alone has fibrinolytic activity; the activators must be liberated before plasmin can be formed (Fig. 3).

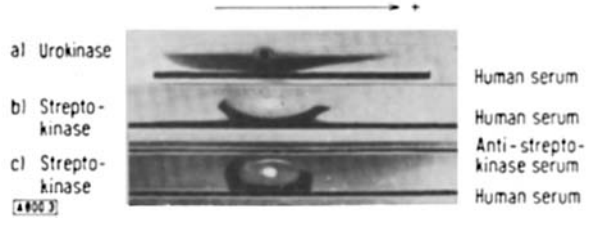


Fig. 3. Detection of plasminogen activators by electrophoresis on fibrin-agar plates and activation of the plasminogen system in human serum (a + b) with simultaneous immunological demonstration (c).

[67] *F. Bachmann, N. Fletcher, N. Alkjaersig,* and *S. Sherry,* Biochemistry *3,* 1578 (1964).

[68] *T. Astrup* and *P. Kok,* Thrombos. Diathes. Haemorrh. *13,* 587 (1965).

[69] *A. J. Johnson,* 10. Kongr. Int. Ges. f. Haemat., Stockholm 1964.

[70] *A. Lesuk, L. Terminiello,* and *J. H. Traver,* Science *147,* 3660 (1965).

It should be mentioned again that human plasminogen changes to plasmin autocatalytically and that the activation of plasminogen can also be catalyzed by trypsin[73]. However, these reactions are of no biological interest.

3.2.2. Two-Step Activation

In addition to the intrinsic activators, which are esterases and convert plasminogen directly into plasmin, certain substances of biological origin are capable of changing proactivators into activators which in turn catalyze the formation of plasmin in a further reaction.

Although the animal organism makes little use of this mechanism, which should therefore be regarded as an exceptional case of plasminogen activation, it is of great interest therapeutically. A kinase having these properties has hitherto only been isolated from ascites cells[74]. The mode of action of streptokinase, one of the many metabolites of β-hemolytic streptococci has been more extensively investigated than that of this lysokinase. For several years streptokinase has been manufactured on an industrial scale by modern fermentation techniques for use in fibrinolytic therapy.

Streptokinase is a protein and has been characterized by the usual methods. It is homogeneous in an ultracentrifuge; it migrates uniformly like an α_2-globulin of human serum during free electrophoresis, immunoelectrophoresis, and polyacrylamide gel electrophoresis. The molecule (molecular weight = 47000) consists of a single peptide chain in which the amino acids are arranged without any intramolecular stabilization afforded by disulfide bridges, because cysteine is absent[57,75,76].

3.2.3. The Mode of Action of Streptokinase

According to the available evidence, streptokinase is not an enzyme: it is neither an esterase like the intrinsic activators nor a protease. Also, it is not affected by treatment with diisopropyl fluorophosphonate[77]. Hence its mode of action must differ from that of urokinase or other intrinsic activators. The fact that animal plasminogen, *e.g.* bovine plasminogen, is not activated by streptokinase agrees with the finding that it is largely specific for human plasminogen[78,79].

A definite amino-acid sequence and conformation of the plasminogen molecule therefore appear necessary for interaction with streptokinase. The activator is the initial product of the reaction between human plasminogen and streptokinase; plasmin is generated only during a second reaction. The activator, which has the physical characteristics of a complex between human plasminogen and

[71] *R. H. Painter* in: Intern. Sympos. Anticoagulants and Fibrinolysis. Lea and Febiger, Philadelphia 1961, p. 351.

[72] *N. Heimburger* and *G. Schwick,* Thrombos. Diathes. Haemorrh. *7,* 432 (1962).

[73] *J. H. Lewis* and *J. H. Ferguson,* Amer. J. Physiol. *170,* 636 (1952).

[74] *H. C. Kwaan,* Thrombos. Diathes. Haemorrh. Suppl. 1 ad *6,* 75 (1961).

[75] *N. Heimburger,* Behringwerk-Mitt. *41,* 84 (1962).

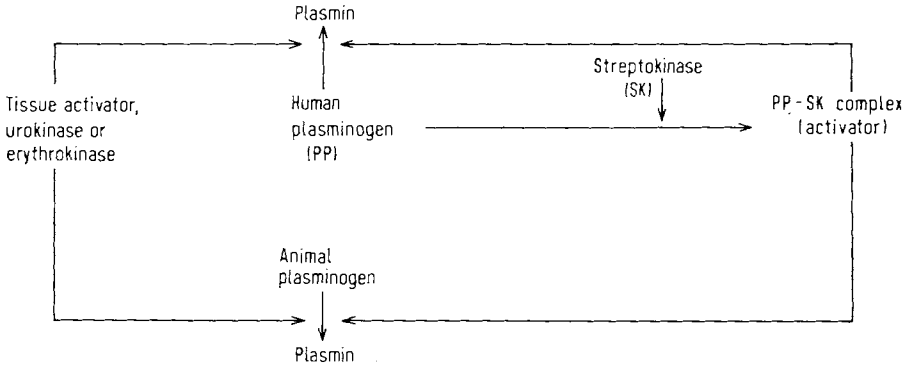
[76] *H. G. Schwick,* Behringwerk-Mitt. *44,* 103 (1964).

[77] *F. Buck* and *E. C. De Renzo,* Biochem. Biophys. Acta *89,* 348 (1964).

[78] *S. Müllertz* and *M. Lassen,* Proc. Soc. Exp. Biol. Med. *82,* 264 (1953).

[79] *S. Müllertz,* Biochem. J. *61,* 424 (1955)

streptokinase, catalyzes the conversion of human and animal plasminogen in a manner comparable with natural activators[56,75] (Scheme 3). For this reason we have proposed the functional term "proactivator-plasminogen" to describe human plasminogen.



Scheme 3. Activation of animal and human plasminogen with endogenous activators and with streptokinase.

Measurement of the rate of hydrolysis of a fibrin clot, prepared by adding thrombin to a solution of fibrinogen, is the basis for assays of activator and plasmin. Clots of bovine fibrin are employed for the estimation of activator. Bovine plasminogen is adsorbed in relatively large quantities by fibrin prepared by the usual methods; activators but not streptokinase convert it into plasmin, as emphasized above. Plasmin, a proteolytic enzyme, is assayed by its hydrolysis of casein or of clots prepared from plasminogen-free fibrinogen. The dilution at which the clot is lyzed in the test solution within 15 min affords a measure of the activity of the activator or plasmin; its reciprocal value is used in the calculation.

The relative amounts of activator and plasmin formed by the catalytic action of streptokinase on human plasminogen can easily be appreciated[80]. Figure 4 is a plot of the results of a series of experiments showing how the activator and plasmin activities are affected by reaction of varying amounts of streptokinase (SK) with a constant amount of human plasminogen (PP). It can be seen that a relatively low proportion of streptokinase is sufficient for catalyzing a maximum formation of plasmin. It is important to realize that with increasing streptokinase concentrations the capacity of the activator increases to the same extent that the plasmin yield decreases. Quantitative stoichiometric evaluation of these results shows that the optimum for plasmin formation is at a molar ratio of plasminogen:

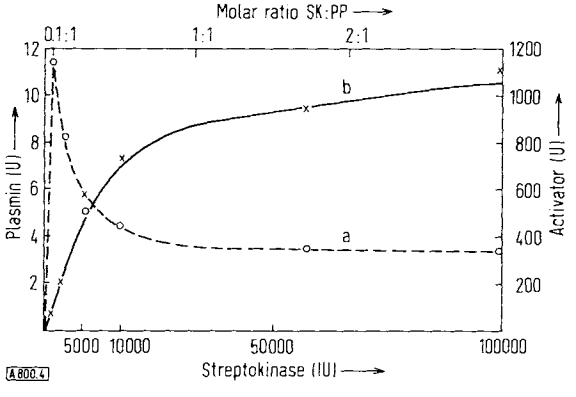


Fig. 4. The capacity of a constant quantity of human plasminogen for plasmin and activator formation as a function of the units of streptokinase used for activation. Determination on clots from pure bovine fibrinogen (a, plasmin) and plasminogen-containing bovine fibrinogen (b, activator). U = units.

streptokinase = 1:0.1, but the activator yield reaches its maximum only when the components are present in equimolar amounts. It might be added that the activator is only weakly proteolytic, in contrast to plasmin. The values obtained under the same conditions by measuring the hydrolysis of casein agree with the above figures[80]. On the basis of these findings we have developed a working hypothesis according to which plasmin loses its proteolytic activity but retains its ability to hydrolyze esters once it is bound to streptokinase to form the activator[57,81].

To prove this hypothesis it is essential that plasmin can be shown to combine with streptokinase in an activator complex. The technique of fibrin-agar electrophoresis enables us to demonstrate this clearly. Streptokinase is first subjected to electrophoresis on a fibrin-agar plate and plasmin that has been prepared by reacting streptokinase and human plasminogen at a molar ratio of 0.2:1 is then allowed to diffuse into the gel from a slit parallel to the direction of electrophoretic separation. An inhibition of the fibrinolytic activity of plasmin may be observed within the zone of migration of the streptokinase. If a solution of bovine serum, which does not react with streptokinase, is dropped onto this inhibition zone a clear halo indicating hydrolysis will appear. This result is not surprising, since the molar ratio of streptokinase to plasminogen reaches a value of 1 where plasmin (molar ratio of the components = 0.2:1) meets streptokinase. Here the conditions for activator formation are optimal, so that only residual proteolytic activity can be detected with casein or plasminogen-free bovine fibrinogen as the substrate (Fig. 4). Such activity cannot be ascribed to the activator with certainty because it is relatively labile and decomposes with the release of plasmin.

Plasmin and activator, which arise by the interaction between human plasminogen and streptokinase, can be

[80] *N. Heimburger* in: Sympos. d. Dtsch. Gesellsch. f. Angiologie, München. Schattauer-Verlag, Stuttgart 1967, p. 7.

[81] *N. Heimburger*, 16th Annual Sympos. on Blood. Detroit, Wayne State Univ., January 1968; Thrombos. Diathes. Haemorrh. *19*, 598 (1968).

characterized by the usual methods of protein chemistry. Polyacrylamide gel electrophoresis is an efficient tool to achieve a clear separation (Fig. 5).

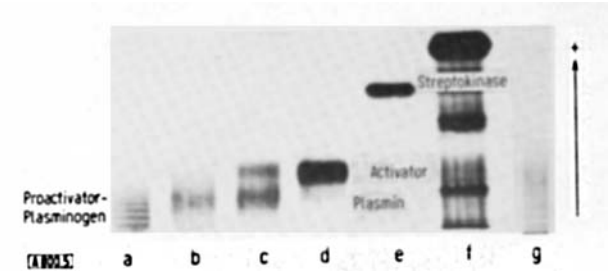


Fig. 5. Polyacrylamide gel electrophoresis. a, human plasminogen (proactivator plasminogen). b, human plasminogen activated by urokinase. c, human plasminogen activated by streptokinase; molar ratio 1 : 0.2. d, human plasminogen activated by streptokinase, molar ratio 1 : 1. e, streptokinase. f, human serum. g, human plasminogen activated by streptokinase, molar ratio 1 : 1, in 8 M urea.

It has been mentioned above that human plasminogen migrates in several bands on polyacrylamide gel electrophoresis although it behaves as a homogeneous protein on paper and immunoelectrophoresis and in the ultracentrifuge. In contrast, plasmin appears almost homogeneous when it has been prepared by activating human plasminogen with urokinase. The electrophoretic pattern of a reaction mixture of streptokinase and human plasminogen (molar ratio = 0.2:1) contains a component with the same mobility as well as a faster one. Since it is known that urokinase only catalyzes the formation of plasmin, the slower moving band can obviously be attributed to plasmin and the faster one to the activator, particularly since an activation mixture consisting of equimolar quantities of the components gives rise to only this one component, which migrates almost exactly between human plasminogen and streptokinase. Plasminogen as well as streptokinase can be demonstrated in this band by immunological methods. This means that the activator behaves like a complex of the two reactants[56]. The molecular weight calculated from sedimentation analysis corresponds to the sum of the molecular weights of plasminogen (or plasmin; cf. Fig. 2) and streptokinase[82].

The activator is a relatively labile intermediate product; for that reason traces of plasmin always appear, whatever its composition. Moreover, the complex remains stable for several days at 0 °C but disintegrates within a few hours at 37 °C[83]. The plasmin formed catalyzes the degradation of the activator by hydrolyzing streptokinase.

The complex is bound together only by physical forces; it disintegrates under conditions where hydrogen bonds are broken, *e. g.* in concentrated solutions of urea. During this dissociation a relatively large amount of plasmin is formed within a short time, which leads to total hydrolysis of streptokinase to form numerous by-products.

All the available evidence supports our concept of the mode of action of streptokinase: the intermediate product of the activation of human plasminogen is a complex held together by hydrogen bonds and hydrophobic forces. As far as its specificity is concerned, it may be compared with the intrinsic activators (Scheme 3); nevertheless, it is not stable but is catalytically decomposed by plasmin in a temperature-dependent reaction. Plasmin and streptokinase combine in the cold to form the activator. Human plasminogen that has previously been inactivated with diisopropyl fluorophosphonate will still bind streptokinase but is no longer biologically active. This indicates that the plasmin and the activator have the same active site, *i.e.* a reactive serine residue[84]. It follows that the activator is actually a modified plasmin which has lost its broad proteolytic action by association with streptokinase, but at the same time has acquired the specificity of intrinsic activators. How this complex is formed from the proenzyme is not yet clear, because streptokinase appears to possess no enzyme activity.

3.2.4. Indirect Activation

Fibrinolysis can be stimulated by many chemically defined substances, with often varying pharmacological efficacy. Such an effect is exhibited by heparin and its derivatives, a wide range of salicylic and nicotinic acid derivatives, hormones including their anabolic forms, and certain antidiabetic drugs[62]. All these have a mode of action about which little is known. They are regarded as indirect fibrinolytic agents, because some of them are not active *in vitro*. Heparin and its derivatives are used extensively in the prophylaxis and therapy of thromboembolic diseases; the nature of the fibrinolytic action of heparin has not yet been discovered. Derivatives of nicotinic acid act by mobilizing endogenous factors, and those of salicylic acid either activate plasminogen or block antiplasmins. The salicylic acid derivatives have widely varying structures and display activities measurable *in vitro*[57,85–87]. It may be assumed that metabolic stimulation and a shift in the metabolic equilibrium constitute the basis of the action of the hormones including their anabolites, and also of antidiabetic drugs[88–91].

4. Inhibitors of Blood Clotting and Fibrinolysis

Both blood clotting and fibrinolysis are under the control of inhibitors that are capable of blocking activation at various stages.

According to a no longer contemporary classification, human serum contains six antithrombins[116], all of them proteins (Table 2). Only two of them are thrombin in-

[82] *E. C. De Renzo,* Thrombos. Diathes. Haemorrh., Suppl. 1 ad *6,* 134 (1961).

[83] *N. Heimburger,* unpublished.

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hibitors in the strictest sense. The functional relationships can be recognized from the nomenclature of the antithrombins.

Table 2. Antithrombins of human serum.

Antithrombin	Origin or action
I	Fibrin (adsorption effect)
II	Heparin cofactor
III	Progressive antithrombin [a]
IV	Reaction product of prothrombin activation
V	Pathological increase of immunoglobulins: antibody
VI	Degradation products of fibrinogen

[a] See also Table 3.

Fibrin has been called antithrombin I because it is capable of binding relatively large amounts of thrombin[92]. Degradation products arising from the action of plasmin on fibrin and fibrinogen are classified as antithrombin VI[93]. Their presence constitutes a diagnostic aid because they are found in blood in cases of pathologically raised fibrinolytic activity. These hydrolysis products act by inhibiting the polymerization of fibrin. It is of particular physiological interest that plasmin is able to split off an antithrombin substance from fibrin, for clotting and fibrinolysis are linked through this reaction in compensatory fashion. Antithrombin IV is set free during prothrombin activation[94] in proportions related to the quantity of thrombin generated. This neutralization of thrombin is based on a feedback mechanism. Antithrombin V[117] is a pathological factor probably identical with an antibody against thrombin.

Antithrombin III[95] and α_2-macroglobulin[96] are the most potent inhibitors found in blood; they are thrombin inhibitors in the strict sense. They were isolated only a few years ago and found to be glycoproteins (Table 3); in Table 2 they are still listed under a general name (antithrombin III or progressive antithrombin), because they could not previously be estimated separately. Together they are capable of inhibiting amounts of thrombin four to five times that present in the blood[97]. It may be recalled that these substances belong to the type of progressive inhibitors which do not neutralize thrombin immediately but progressively at a rate of inactivation that is constant during the first few minutes. Heparin accelerates the neutralization of thrombin by antithrombin very considerably by catalysis. In Table 2 this effect is listed as antithrombin II or heparin cofactor; originally it had been ascribed to another protein before we were able to show that antithrombin II and III are identical proteins[95].

The following proteinase inhibitors present in human serum, listed together with their physical and chemical properties in Table 3, have antiplasmin action: α_1-antitrypsin, antithrombin III, the $C\bar{1}$-inactivator, and α_2-macroglobulin. All these received their names from the most important or the first biological property discovered (Table 4).

Table 4. Enzymic specificity of inhibitors.

Inhibitors	Enzymes inhibited					
	trypsin	chymotrypsin	plasmin	thrombin	kallikrein	$C\bar{1}$-esterase
α_1-Antitrypsin	+	+	+	–	+	–
α_1-Antichymotrypsin	–	+	–	–	–	–
Inter-α-trypsin inhibitor	+	weak	–	–	–	–
Antithrombin III	+	–	+	+	–	–
$C\bar{1}$-inactivator	weak	weak	+	–	+	+
α_2-Macroglobulin	+	+	+	+	+	–

α_2-Globulins account for *ca.* 10% of the antiplasmin activity of human serum. α_1-Antitrypsin is the most important antiplasmin – it inactivates plasmin irreversibly like a progressive inhibitor. Human serum is capable of ex-

Table 3. Concentration and properties of inhibitors in human serum.

Inhibitors	Conc. in human serum		Molecular weight	Peptide content (%)	Carbohydrate content (%)
	mg/100 ml	μ mole			
α_1-Antitrypsin	290.0 + 45.0	54.0	54000	86	12.2
α_1-Antichymotrypsin	48.7 + 6.5	7.0	69000	73	24.6
Inter-α-trypsin inhibitor	50.0	3.1	160000	90	8.4
Antithrombin III	29.0 + 2.9	4.5	65000	85	13.4
$C\bar{1}$-inactivator	23.5 + 3.0	2.3	104000	65	34.7
α_2-Macroglobulin	260.0 + 70.0	3.3	820000	92	7.7
	701.2				

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hibiting 30 times as much antiplasmin activity as potential plasmin activity.

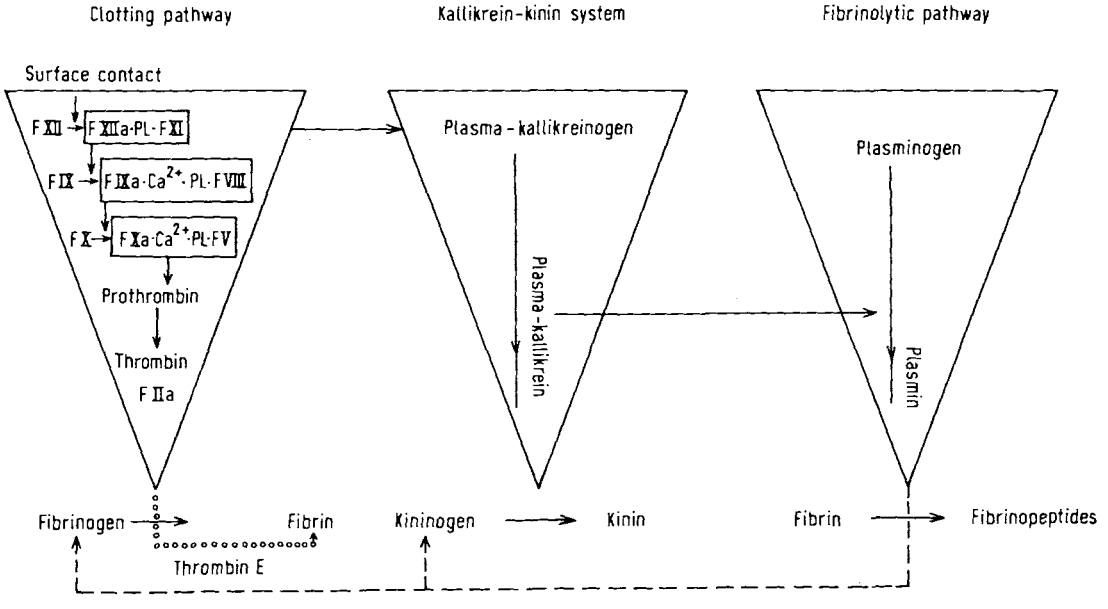
Two of the plasmin inhibitors, α_2-macroglobulin and antithrombin III, also possess thrombin specificity, an observation which is of particular physiological interest. Hence these two proteins are able to control the equilibrium between clotting and fibrinolysis: the quantity expended during an increased release of thrombin is compensated by its not being available as an antiplasmin. The biological result is an increase in fibrinolysis.

The lack of specificity of proteinase inhibitors present in the blood is a phenomenon exploited by the body for the regulation of other proteolytically controlled reactions. These proteinases have many amino-acid sequences in common, including those at the active site, thus making them broadly specific[99]. This fact applies to trypsin, thrombin, chymotrypsin, and elastase; a phylogenetic relationship is obviously expressed. Therefore, it appears only logical that the reactions regulated proteolytically in the blood are also linked through these enzymes.

It can be seen in Scheme 4 that the Hageman factor (F XII) activates not only the coagulating but also the fibrinolytic mechanism[100,101] and the kallikrein-kinin system[102–106]. Neither thrombin nor plasmin are strictly specific enzymes: thrombin converts fibrin into fibrinogen and hydrolyzes fibrin as thrombin E[45,118]. Plasmin is known to hydrolyze fibrin and fibrinogen while at the same time setting free antithrombin VI which blocks the polymerization of fibrin. Finally, plasmin is capable of catalyzing the liberation of kinins from kininogen, an α_2-globulin of human plasma[107]. Here too the reaction product is biologically highly active, since it is a vasodilator, increases capillary permeability, and promotes the migration of leukocytes[108]. These events characteristic of inflammations demonstrate how a narrowly circumscribed biological phenomenon can express itself through many complicated chemical reactions. It should be mentioned that clotting factors I, V, and VIII are initially inactivated when fibrinolysis overshoots, but antiplasmins prevent the attack by plasmin on other plasma proteins or biological factors.

Inactivation and also generation (antithrombin VI) of clotting factors should be looked upon as biological measures designed to prevent reclotting after fibrinolysis. Finally, it should be stressed once more that the broad specificity of proteinases in blood is apparent in all these reactions.

Various drugs may intervene in the processes just described. Prothrombin synthesis may be influenced by vitamin K antagonists of the dicoumarol type, and complexing agents can prevent clotting because the calcium ion is the essential catalyst of the most important stages of the clotting mechanism.



Scheme 4. Interaction of physiologically important enzyme systems in blood.

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5. Biochemical Aspects of Thrombolysis Therapy

Heparin is administered in the conventional treatment of thrombosis. It is known to accelerate catalytically the neutralization of thrombin by antithrombin III, and thus prevent reclotting following fibrinolysis. A lipoprotein lipase with the functional name of "clearing factor" is released following an injection of heparin[109–113]. The nature of the effect of heparin on the fibrinolytic mechanism is still unknown.

The fact that thrombosis is a vascular occlusion consisting predominantly of fibrin and therefore accessible to proteolysis suggests the following therapeutic possibilities: local application of enzymes to hydrolyze the clot; infusion therapy with enzymes; infusion therapy with fibrinolysis activators.

For local application the clot should be compact and accessible, so that the activator or enzyme solution can reach it through the catheter, thus by-passing inhibitors in the plasma. The reason why activators by themselves are so effective is the relatively large quantity of plasminogen that is adsorbed on the fibrin of the clot. Intrinsic substances such as plasmin are most suitable as enzymatic hydrolyzing agents, because immunologically foreign enzymes may stimulate the production of antibodies.

Treatment of thrombosis by injecting proteases at a distant site has little chance of success. The level of proteinase inhibitors in blood is too high, and it would not be sound biological sense to take a gamble. A generalized proteolysis would be the result, because proteinases are not sufficiently specific.

Infusion therapy with activators has been well tested clinically; in fact, the mechanism is found in the body. At first the obvious attempt was made to use endogenous urokinase for treatment, but experiments have shown that as much as 400 liters of urine yield only a single dose for treatment. Thus preparation of urokinase requires the manipulation of large volumes of urine which, owing to the limited stability of urokinase, must be processed fairly quickly and by applying complicated methods. These procedures make urokinase very costly and it is not yet available in amounts sufficient for therapy. In the meantime, the use of streptokinase has been developed. Now, ten years later, the necessary experimental and clinical experience is available for using streptokinase in treatment[114]: the indications and contraindications are known; with the exception of a few special cases, the dosage has been largely standardized and with it supervision of treatment.

Acute arterial and venous occlusions have proved to be sure and early indications. There are now pointers that so-called chronic arterial occlusions, several months old, can be treated by hydrolyzing the clot[115] (Fig. 6). Recent heart infarctions promise to become another important indication.

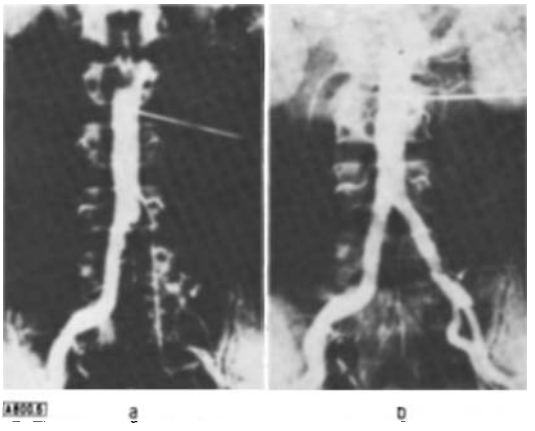


Fig. 6. Chronic obliteration of the common iliac artery and the femoral artery (left) a) before and b) after treatment with streptokinase (X-ray photograph by Dr. *M. Martin*, Aggertalklinik, Engelskirchen, Germany).

The dose of streptokinase is chosen so that the activator is the predominant product. Application is by infusion through continuous drip lasting several days. The advantage of this method of administration is that the hemostatic equilibrium remains largely undisturbed. A short period of plasminemia occurs at the beginning of the treatment, until the plasminogen and streptokinase are present in equimolar proportions. That is why a prolongation of the plasma thrombin time may be observed shortly after the onset of thrombolysis, which has been caused by the release by plasmin of antithrombin VI from fibrinogen. When the thrombin time becomes normal again after 4–6 h, the fibrinolysis is known to proceed smoothly.

Research on fibrinolytic agents tends toward finding oral prophylactics against thrombosis in the hope of bringing these endeavors to a successful conclusion.

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New Methods for the Synthesis of Vinyl Azides

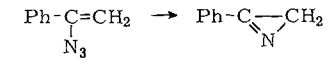
By Gerrit L'abbé and Alfred Hassner[*]

A critical survey of synthetic approaches to vinyl azides is presented, focusing especially on stereo- and regiochemical problems. The combined procedure of azidohalogenation of olefins followed by dehydrohalogenation, leads to regiospecific and, in the case of ionic additions, also to stereospecific formation of vinyl azides. Nucleophilic substitutions by azide ions on activated olefinic halides result in β-azidovinyl ketones, esters, nitriles, etc., and proceed predominantly with retention of configuration about the C=C bond. The known synthetic methods leading to α-azidovinyl ketones and esters give rise to the thermodynamically more stable trans-vinyl azides.

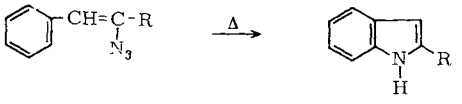
1. Introduction

During the last few years unsaturated azides have acquired considerable importance as intermediates in organic syntheses and new methods for their preparation have been devised. It is remarkable that vinyl azide (CH_2=CHN_3), the simplest of this class of unsaturated azides, was first described in 1910[1], yet most of the knowledge concerning the synthesis and reactions of these compounds has been gained during the past five years. The reason for interest in this class of compounds is the high reactivity of the azide function which is susceptible to photolysis, pyrolysis, cycloadditions and attack by nucleophiles as well as by electrophiles[2]. The presence of a neighboring double bond accentuates the reactivity of the azide group and provides additional intramolecular pathways for reaction. A few examples are shown below.

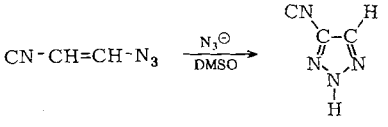
Among the recently studied transformations of vinyl azides are their pyrolysis[3] and photolysis[4] which serve as a general method of synthesis of azirines, a heretofore rare class of heterocycles.

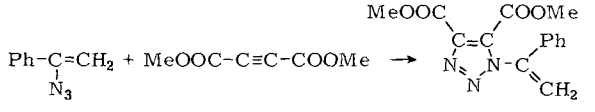


Pyrolysis of some vinyl azides has furnished indole derivatives[3b,5].

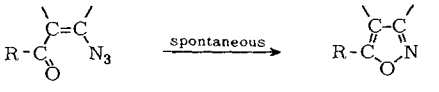


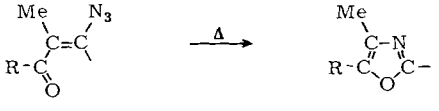
Examples of intramolecular[6] and of intermolecular[7] cycloadditions have been reported.



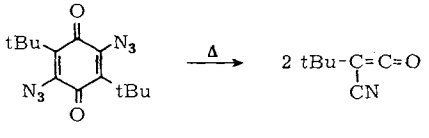


Formation of the heterocycles isoxazoles and oxazoles can likewise be accomplished *via* unsaturated azides[8].





The most recent synthetic application of vinyl azides is the synthesis of a reactive ketene in pure form[9].



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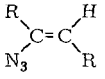
[8] *M. I. Rybinskaya*, *A. N. Nesmeyanov*, and *N. K. Kochetkov*, Usp. Khim. *38*, 961 (1969); Russian Chem. Rev. *38*, 433 (1969).

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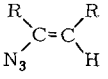
A few remarks about nomenclature are in place here. Though the term vinyl azide strictly applies to $CH_2=CHN_3$, it has been generally adopted, and hence is used in this review to denote any α,β-unsaturated azide. In addition to these two terms, that of enazide has been employed on occasion.

In this review we will discuss methods leading to the synthesis of vinyl azides. For convenience the topics have been divided according to the type of substituents present on the double bond.

Another aspect that will be emphasized is the stereochemistry and regiochemistry of these compounds. The *stereochemistry* refers to the configuration of substituents about the C=C bond, *i.e. cis* and *trans* compounds are to be differentiated.



trans

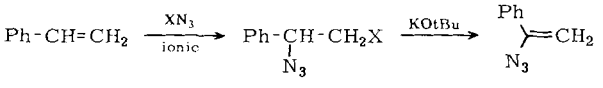


cis

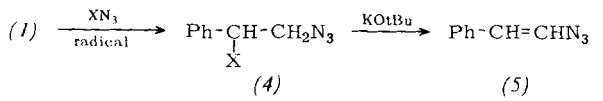
Regiochemistry refers to directional preference in bond making or breaking[10] and in the case under study indicates the point of attachment of the azide function on the C=C bond, *i.e.* $R-CN_3=CH_2$ and $R-CH=CHN_3$ are *regioisomers.*

2. Simple Vinyl Azides[*]

A general synthetic method for vinyl azides, discovered by *Hassner et al.*[11], involves the addition of halogen azides to olefins, followed by treatment of the resulting β-haloalkyl azides with a base such as potassium *tert*-butoxide, sodium methoxide, or 1,4-diazabicyclo[2.2.2]-octane. The addition of halogen azides can occur by either an ionic or a free radical process and leads to regioisomeric vinyl azides as illustrated below in the case of styrene [*i.e. (1)* → *(2)* → *(3)* or *(1)* → *(4)* → *(5)*].



(1) *(2)* *(3)*



(4) *(5)*

An ionic pathway in the XN_3 addition is favored in a polar medium (*e.g.* acetonitrile, nitromethane, DMF) and in the presence of oxygen (a free radical inhibitor), whereas a free radical pathway is enhanced in a solvent of low polarity (*e.g.* pentane), in the presence of light, and in the absence of oxygen. Furthermore, it has been shown that the preference of the halogen azides for homolytic cleavage increases in the order: $IN_3 < BrN_3 < ClN_3$. Hence the conditions for an exclusive ionic or free radical reaction can be readily adjusted in the case of BrN_3, whereas IN_3 reacts preferentially by an ionic path and ClN_3 by attack of the N_3 radical on the double bond.

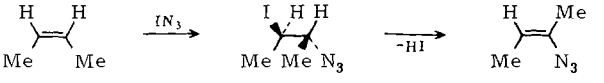
[*] By simple vinyl azides we designate those compounds lacking functional groups such as C=O, CN, F, *etc.*

2.1. Ionic Addition

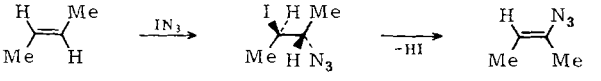
The ionic additions of IN_3 to olefins occur stereospecifically *anti*[*] *via* a cyclic halonium ion *(6)*, as was clearly shown by the exclusive formation of the *threo-(8)* and *erythro*-2-azido-3-iodobutane *(11)*, respectively, from *cis-(7)* and *trans*-2-butene *(10)*[11a].



(6)

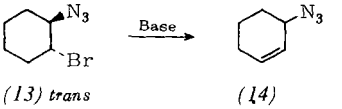


(7) cis *(8) threo* *(9) trans*

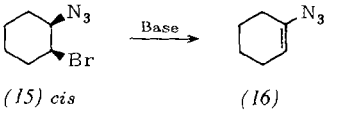


(10) trans *(11) erythro* *(12) cis*

cis- and *trans*-Stilbene gave similar results, cyclohexene was transformed into the *trans* adduct, and 2-cholestene afforded the *trans*-diaxial adduct. The *threo*- and *erythro*- adducts *(8)* and *(11)* are dehydrohalogenated in an *anti* fashion by potassium *tert*-butoxide to give the *trans*- and *cis*-vinyl azides *(9)* and *(12)*, respectively. In most cases the transition state for *anti*-dehydrohalogenation to the vinyl azide is of lower energy than that leading to the allyl azide; hence regiospecific elimination of HX to the vinyl azide is usually observed. An exception is provided by *trans*-halocycloalkyl azides (in rings with less than eight members) which lead to allyl azides, *i.e. (14)*. The *cis*-isomer *(15)* furnishes *(16)*. In eight-membered rings *syn* elimination to a vinyl azide occurs.



(13) trans *(14)*



(15) cis *(16)*

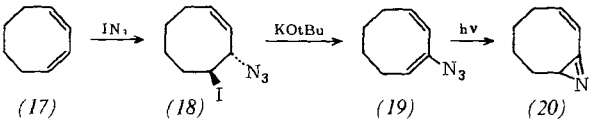
The regiochemistry of most ionic additions is controlled by electronic effects operating in the cyclic intermediate *(6)*. Thus 1,3-cyclooctadiene *(17)* adds IN_3 to give adduct *(18)* in 72% yield. Elimination of HI from *(18)* oc-

[*] The terms *cis* and *trans* are used for configurational assignments, and *syn* and *anti* for describing transformations during chemical processes.

[10] *A. Hassner*, J. Org. Chem. *33*, 2684 (1968).

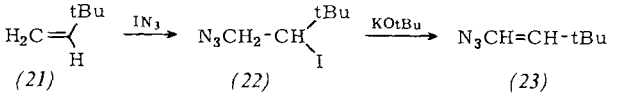
[11] a) *A. Hassner* and *L. A. Levy*, J. Amer. Chem. Soc. *87*, 4203 (1965); *F. W. Fowler, A. Hassner*, and *L. A. Levy, ibid. 89*, 2077 (1967); b) *A. Hassner* and *F. W. Fowler*, J. Org. Chem. *33*, 2686 (1968); c) *A. Hassner* and *F. Boerwinkle*, J. Amer. Chem. Soc. *90*, 216 (1968); d) *A. Hassner* and *F. Boerwinkle*, Tetrahedron Lett. *1969*, 3309; e) *A. Hassner, F. P. Boerwinkle*, and *A. B. Levy*, J. Amer. Chem. Soc. *92*, 4879 (1970); f) *A. Hassner*, Accounts Chem. Res., in press.

curs regiospecifically and *syn*, yielding the *cis,cis*-azidocyclooctadiene *(19)*. Photolysis of *(19)* leads to the fused azirine *(20)*[4b].



(17) *(18)* *(19)* *(20)*

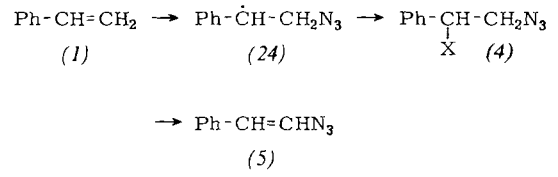
An exception to the generally observed mode of addition (electronic control) is the IN_3 addition to 3,3-dimethyl-1-butene *(21)*, where a pure steric effect accounts for the exclusive formation of 1-azido-2-iodo-3,3-dimethylbutane *(22)* which, on treatment with potassium *tert*-butoxide, furnishes the 1-azide *(23)*[11b].



(21) *(22)* *(23)*

2.2. Radical Addition

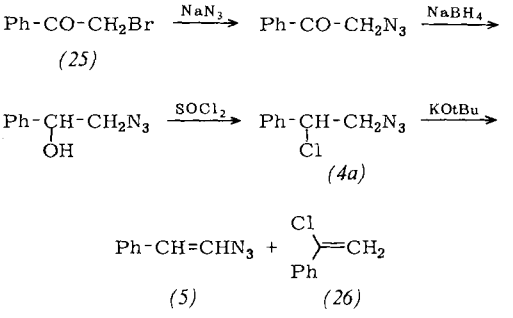
The radical additions of halogen azides occur *via* a free radical intermediate such as *(24)* (for styrene) with the result that no stereospecific addition to *cis*- and *trans*-olefins can be expected.



(1) *(24)* *(4)* *(5)*

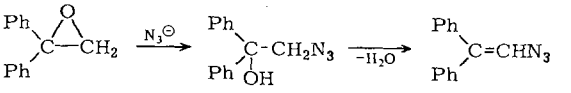
Indeed, the addition of BrN_3 to 2-cholestene under free radical conditions led to a mixture of two 1:1 adducts, one *trans*-diaxial and the other *cis*. Another example is the ferric ion catalyzed radical addition of ClN_3 to cyclohexene for which a *trans : cis* ratio of 70/30 is reported[12].

Previous to the discovery of the free radical method, *trans*-β-azidostyrene *trans-(5)* was only available by a more expensive and time-consuming sequence starting from phenacyl bromide *(25)* with the formation of *(26)* as a side product[13].



(25) *(4a)* *(5)* *(26)*

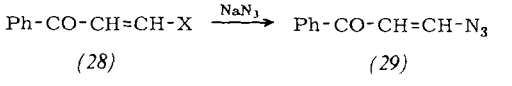
Finally, another method that has been used in the synthesis of some vinyl azides involves the opening of an epoxide by NaN_3, followed by dehydration, as exemplified for 2-azido-1,1-diphenylethylene *(27)*[3b,14].



(27)

3. β-Azidovinyl Ketones, Esters, Nitriles, *etc.*

It is well known that simple vinyl halides are extremely resistant to nucleophilic substitution. However, when the vinylic halide is activated by an electron-withdrawing group in the β-position, halide substitution occurs readily[8,15]. Therefore, β-halovinyl ketones *(28)* are suitable starting materials for the synthesis of β-azidovinyl ketones *(29)*[16].



(28) *(29)*

X = Cl, Br, $\overset{\oplus}{N}H_3Cl^{\ominus}$, NO_2

X ≠ $SO_3^{\ominus}$, CN

Nesmeyanov and *Rybinskaya*[8,17] found that the substitution proceeds predominantly with retention of configuration about the CC double bond[18]. The stereochemical results are compatible with a conjugate addition of the azide ion to the X-carrying carbon of *(28)*, followed by a fast elimination of X^-. The two alternative possibilities — addition of HN_3 followed by elimination of HX or elimination of HX followed by addition of HN_3 — are excluded since the stereochemical results of the reaction would be independent of the configuration of the starting olefin.

It is noteworthy that the *cis*-β-azidovinyl ketone [*cis-(29)*] cannot be isolated in the free form from the reaction of the *cis*-β-halovinyl ketone [*cis-(28)*] and NaN_3, since it decomposes spontaneously to the isoxazole *(30)*. 1-Acetyl-2-chloro-1-cyclopentene *(31)*, which obviously has both substituents in the *cis*-position, is like-

[12] a) *F. Minisci, R. Galli,* and *M. Cecere,* Chim. Ind. (Milan) *48,* 347 (1966); b) *F. Minisci, ibid. 49,* 705 (1967).

[13] a) *J. H. Boyer, W. E. Krueger,* and *G. J. Mikol,* J. Amer. Chem. Soc. *89,* 5504 (1967); b) *J. H. Boyer, W. E. Krueger,* and *R. Modler,* J. Org. Chem. *34,* 1987 (1969).

[14] *K. Ponsold* and *G. Schubert,* J. Prakt. Chem. *311,* 919 (1969).

[15] *A. E. Pohland* and *W. R. Benson,* Chem. Rev. *66,* 161 (1966).

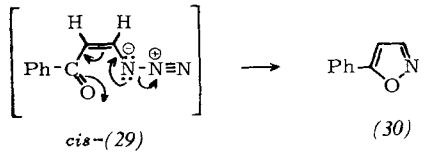
[16] *P. Beltrame, G. Favini, M. G. Cattania,* and *F. Guella,* Gazz. Chim. Ital. *98,* 380 (1968).

[17] a) *A. N. Nesmeyanov* and *M. I. Rybinskaya,* Izv. Akad. Nauk SSSR, Otd. Khim. Nauk *1962,* 816; Bull. Acad. Sci. USSR, Dir. Chem. Sci. *1962,* 761; b) *A. N. Nesmeyanov* and *M. I. Rybinskaya,* Dokl. Akad. Nauk SSSR *170,* 600 (1966); Proc. Acad. Sci. USSR *170,* 916 (1966); c) *A. N. Nesmeyanov, M. I. Rybinskaya,* and *T. G. Kelekhsaeva,* Zh. Org. Khim. *4,* 921 (1968); J. Org. Chem. USSR *4,* 897 (1968); d) *A. N. Nesmeyanov, M. I. Rybinskaya,* and *T. G. Kelekhsaeva,* Izv. Akad. Nauk SSSR, Ser. Khim. 866 (1969); Chem. Abstr. *71,* 21495w (1969).

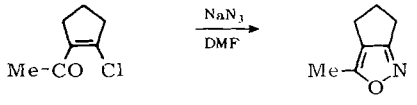
[18] The mechanism explaining retention of configuration in nucleophilic substitution on olefinic halides is discussed by: *E. L. Eliel,* "Stereochemistry of Carbon Compounds", McGraw-Hill Book Company, Inc. New York, 1962, p 369.

[19] *S. Maiorana,* Ann. Chim. (Rome) *56,* 1531 (1966).

wise converted by NaN_3 to the isoxazole *(32)*[19]. Whether isoxazole formation proceeds *via* a nitrene or by a concerted mechanism [as shown for *cis-(29)*] has not been established.

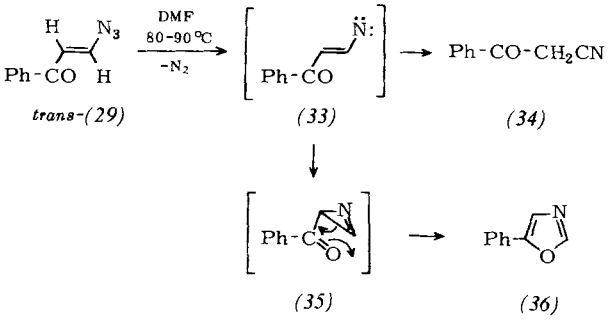


cis-(29) *(30)*



(31) *(32)*

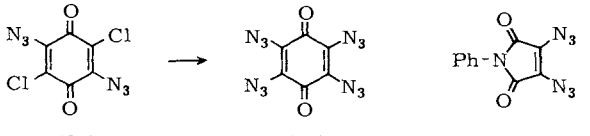
Unlike their *cis*-analogs, *trans*-β-azidovinyl ketones [*e.g. trans-(29)*] are stable under ordinary conditions and only decompose on heating into nitriles *(34)* and oxazoles *(36)*[20]. The reaction probably proceeds *via* a nitrene *(33)*, which is converted either to the nitrile *(34)* or *via* an azirine *(35)* to the oxazole *(36)*:



trans-(29) *(33)* *(34)* *(35)* *(36)*

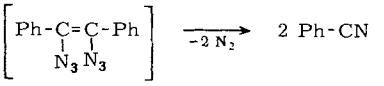
The formation of different products in the decomposition of *cis*- and *trans*-β-azidovinyl phenyl ketones *(29)* (isoxazoles *versus* nitriles and oxazoles) was used by *Nesmeyanov* and *Rybinskaya*[8, 17] as a criterion for elucidating the geometrical structure of the vinyl azides *(29)*.

Azidoquinones[21] [*e.g. (37)* and *(38)*] and azidomaleimides[22] [*e.g. (39)*] are structurally related to *trans*-azidovinyl ketones and are therefore readily prepared from the corresponding chloro derivatives.



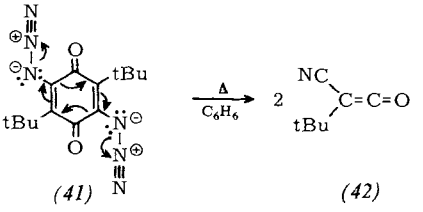
(37) *(38)* *(39)*

Unlike their cyclic analogs, the open-chain vinyl α, β-bisazides, *e.g. (40)*, are unstable and decompose to nitriles[23].

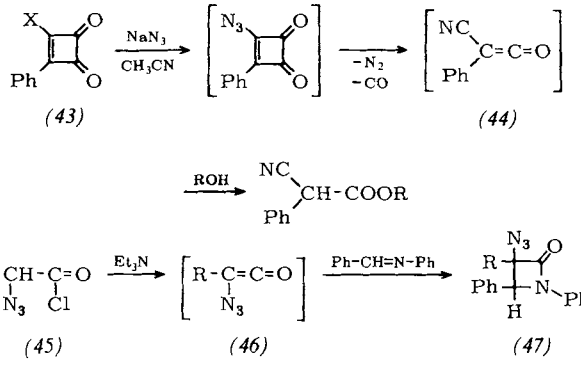


(40)

2,5-Bisazido-3,6-di-*tert*-butyl-1,4-benzoquinone *(41)* undergoes a thermal fragmentation in refluxing benzene to give two molecules of the thermally stable, yet very reactive, *tert*-butyl cyanoketene *(42)*[9]. The decomposition reaction is comparable to the formation of phenyl cyanoketene *(44)* by reacting 3-halo-4-phenylcyclobutenedione *(43)* with NaN_3 in acetonitrile[24]. Ketene *(44)*, however, was only prepared *in situ* and was subsequently trapped by hydroxylic compounds. It is also noteworthy that azidoketenes *(46)* can be prepared *in situ* by dehydrohalogenation of *(45)* and can be trapped with Schiff bases to give azetidinones *(47)*[25].



(41) *(42)*



(43) *(44)* *(45)* *(46)* *(47)*

Modena and *Todesco*[26] reported that the reaction of both *cis*- and *trans*-β-chlorovinyl arylsulfones *(48)* with NaN_3 proceeds with retention of configuration and follows a second order rate law. Their kinetic results clearly indicate that the reaction rate is only slightly influenced by the geometrical structure of the starting olefin. Substituents in the phenyl ring, on the contrary, affect the rate profoundly and to the same extent for *cis*- as for *trans*-olefins. A plot of log k_2 *versus* σ gives two parallel lines with a ρ-value of +1.84, thereby demonstrating the accelerating effect of electron-withdrawing substituents.

[20] For photolysis of β-azidovinyl ketones see: *S. Sato*, Bull. Chem. Soc. Jap. *41*, 2524 (1968).

[21] a) *K. Fries* and *P. Ochwat*, Ber. dtsch. chem. Ges. *56*, 1291 (1923); b) *L. F. Fieser* and *J. L. Hartwell*, J. Amer. Chem. Soc. *57*, 1482 (1935); c) *J. A. Van Allan, W. J. Priest, A. S. Marshall*, and *G. A. Reynolds*, J. Org. Chem. *33*, 1100 (1968); d) *H. W. Moore, H. R. Shelden, D. W. Deters*, and *R. J. Wikholm*, J. Amer. Chem. Soc. *92*, 1675 (1970).

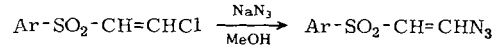
[22] a) *A. Mustafa, S. M. A. D. Zayed*, and *S. Khattab*, J. Amer. Chem. Soc. *78*, 145 (1956); b) The structure assignment for *(39)* by the above authors has been incorrectly interpreted and criticized by: *W. I. Awad, S. M. A. R. Omran*, and *F. Nagieb*, Tetrahedron *19*, 1591 (1963).

[23] *A. Hassner, R. J. Isbister*, and *A. Friederang*, Tetrahedron Lett. *1969*, 2939.

[24] a) *R. C. De Selms*, Tetrahedron Lett. *1969*, 1179; b) *A. H. Schmidt* and *W. Ried, ibid. 1969*, 2431.

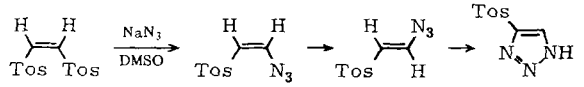
[25] a) *A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya*, and *M. S. Manhas*, Tetrahedron *23*, 4769 (1967); b) *M. S. Manhas, J. S. Chib, Y. H. Chiang*, and *A. K. Bose, ibid. 25*, 4421 (1969); c) *A. Hassner, R. J. Isbister, R. B. Greenwald, J. T. Klug*, and *E. C. Taylor, ibid. 25*, 1637 (1969).

[26] *G. Modena* and *P. E. Todesco*, Gazz. Chim. Ital. *89*, 866 (1959).



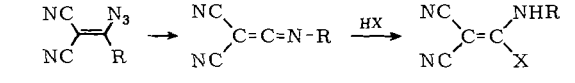
(48) (49)

Meek and *Fowler*[27] investigated the reaction of *cis*- and *trans*-1,2-ditosylethylene *(50)* with NaN_3 in several solvents, and their stereochemical findings [retention of configuration for *(50)*→*(51)*] agree with those of *Modena* and *Todesco*. In addition they found that *cis-(51)* is formed from *cis-(50)* in the early stage (3 min) of the reaction in DMSO, but it isomerizes into *trans-(51)* within 30 minutes. On standing for a longer time (24 h) in DMSO under the basic conditions (N_3^-), *trans-(51)* cyclizes to the triazole *(52)*. Evidently, the acidic hydrogen atom α to the sulfone in *trans-(51)* is removed under the basic reaction conditions, resulting in cyclization to the aromatic triazole *(52)*.



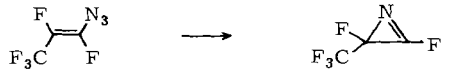
cis-(50) *cis-(51)* *trans-(51)* *(52)*

The generality of the synthetic method described in this section is further substantiated by the facile conversion of β-halovinyl nitriles[28] and fluorides[29] into the corresponding azides, *e.g. (53)* and *(55)*, at 0° C. Both *(53)* and *(55)* decompose at room temperature, the former yielding a ketenimine *(54)* and the latter an azirine *(56)*. The ketenimine was not isolated in the free form but its presence was inferred from trapping experiments.



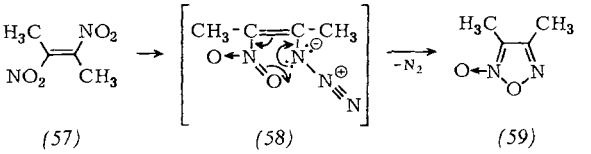
(53) *(54)*

R = H, Me, Ph HX = HCl, EtOH, $PhNH_2$



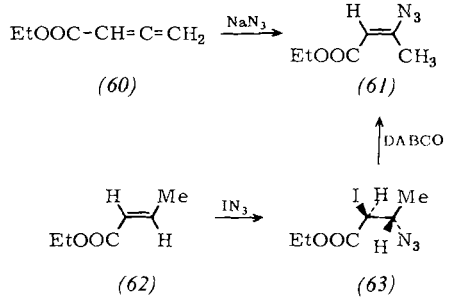
(55) *(56)*

When the β-position is activated by a nitro group as in the case of α-nitro-β-iodoolefins or α,β-dinitroolefins, the corresponding α-nitro-β-azidoolefins, *e.g. (58)*, are not isolated but instead give rise to furoxanes in high yields[30]. The conversion of *trans*-2,3-dinitro-2-butene *(57)* by NaN_3 into 3,4-dimethylfuroxane *(59)* is a typical example.



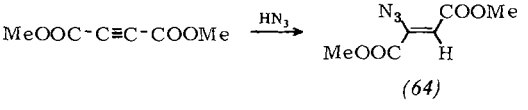
(57) *(58)* *(59)*

Recently, β-azidovinyl esters [*e.g. (61)*] and amides were prepared by treating allenic esters [*e.g. (60)*] and amides with an excess of NaN_3[31]. Although the stereochemistry of the reaction was not elucidated by the authors, structure *(61)* is suggested since the same product was obtained by *Hassner*'s method from ethyl crotonate *(62)*[11b] (DABCO = 1,4-diazabicyclo[2.2.2]octane).



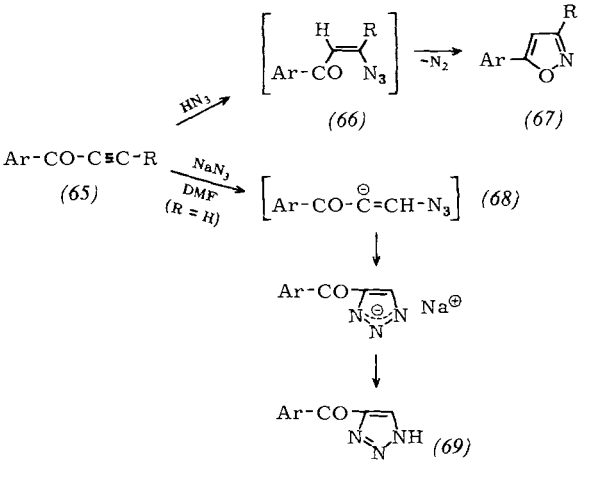
(60) *(61)* *(62)* *(63)*

vic-Triazoles[32] and isoxazoles[33] normally result from the addition of HN_3 and NaN_3 to acetylenes, and only in a few cases[33,34], *e.g.* methyl azidofumarate *(64)*, have vinyl azides been obtained.



(64)

The isoxazoles *(67)* are obtained when acetylenic ketones *(65)* are treated with HN_3, and their formation is probably a result of decomposition of *cis*-β-azidovinyl



(65) *(66)* *(67)* *(68)* *(69)*

[27] *J. S. Meek* and *J. S. Fowler*, J. Amer. Chem. Soc. *89*, 1967 (1967); J. Org. Chem. *33*, 985 (1968).

[28] *K. Friedrich*, Angew. Chem. *79*, 980 (1967); Angew. Chem. internat. Edit. *6*, 959 (1967).

[29] a) *C. S. Cleaver* and *C. G. Krespan*, J. Amer. Chem. Soc. *87*, 3716 (1965); b) *R. E. Banks* and *G. J. Moore*, J. Chem. Soc. *C. 1966*, 2304; c) *C. G. Krespan*, J. Org. Chem. *34*, 1278 (1969).

[30] a) *W. D. Emmons* and *J. P. Freeman*, J. Org. Chem. *22*, 456 (1957); b) *T. E. Stevens* and *W. D. Emmons*, J. Amer. Chem. Soc. *80*, 338 (1958).

[31] a) *G. R. Harvey* and *K. W. Ratts*, J. Org. Chem. *31*, 3907 (1966); b) *G. R. Harvey*, US-Pat. 3471523 (1969), Chem. Abstr. *72*, 3252f (1970).

[32] a) *O. Dimroth* and *G. Fester*, Ber. dtsch. chem. Ges. *43*, 2219 (1910); b) *E. Oliveri-Mandala* and *A. Coppola*, Gazz. Chim. Ital. *40* II, 435 (1910); c) *R. Hüttel*, Ber. dtsch. chem. Ges. *74*, 1680 (1941); d) *J. C. Sheehan* and *C. A. Robinson*, J. Amer. Chem. Soc. *71*, 1436 (1949); e) *L. W. Hartzel* and *F. R. Benson*, *ibid. 76*, 667 (1954); f) *A. N. Nesmeyanov* and *M. I. Rybinskaya*, Dokl. Akad. Nauk SSSR *158*, 408 (1964); Proc. Acad. Sci. USSR *158*, 902 (1964).

[33] a) *U. Türck* and *H. Behringer*, Chem. Ber. *98*, 3020 (1965); b) *A. N. Nesmeyanov* and *M. I. Rybinskaya*, Zh. Org. Khim. *2*, 2081 (1966); J. Org. Chem. USSR *2*, 2041 (1966).

[34] *V. G. Ostroverkhov* and *E. A. Shilov*, Ukrain. Khim. Zh. *23*, 615 (1957), Chem. Abstr. *52*, 7828d (1958).

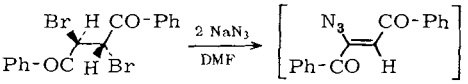
ketones *(66)*, produced initially. Interestingly, when the acetylenic ketones *(65)* are allowed to react with NaN_3 in an aprotonic solvent, such as DMF, no isoxazoles, but triazoles *(69)*, are obtained in high yields. This is logical if one considers the reaction as proceeding *via* the carbanionic intermediate *(68)* which, in the absence of a proton source, cyclizes to the stable aromatic triazole ring *(69)*. This result is similar to that discussed above for vinyl sulfones. Further support for this interpretation is provided by the fact that *trans-(29)* is also converted by NaN_3 in DMF *via (68)* into benzoyl-1,2,3-triazole *(69)*[19]

4. α-Azidovinyl Ketones and Esters

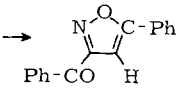
A general synthetic method for α-azidovinyl ketones *(76)* involves the reaction of α,β-dibromoketones *(70)* with two equivalents of NaN_3 in DMF at room temperature[35,36]. A detailed mechanistic study on three α, β-dibromoketones, using NMR techniques, revealed that the reaction proceeds through pathway *(70)→(71)→(73)→(74)→(76)*. Sodium azide in DMF eliminates HBr from *(70)* to give *cis*-bromovinyl ketone *(71)* which isomerizes more or less readily to the *trans*-isomer under the reaction conditions. Both geometrical isomers are converted to the bromo azide *(73)*, *via* intermediate *(72)*, by NaN_3 in the presence of the proton source HN_3. Compound *(73)* then undergoes further nucleophilic substitution by azide ion to give the unstable bis-azide *(74)*, which, on elimination of HN_3, yields the thermodynamically most stable *trans*-α-azidovinyl ketone *(76)*. It was further observed that when R' = Ph, the direct conversion of *(71)* to *(76)* *via* intermediate *(77)* competes with the sequence *(71)→(73)→(74)→(76)*. Both the activation of the α-carbon in *(71)* by the carbonyl group and the stabilization of the negative charge in *(77)* by the phenyl group provide the driving force of the competing reaction *(71)→(76)*.

From the mechanism outlined above, it is obvious that α-bromovinyl ketones *(71)* and the BrN_3 or IN_3 adducts of α,β-unsaturated ketones, *e.g. (73)*, are also starting materials for the synthesis of the α-azidovinyl ketones *(76)*[36]. All three synthetic methods afford *(76)* in high yields.

Under the same reaction conditions, *meso*-1,2-dibenzoyl-1,2-dibromoethane *(78)* gives 3-benzoyl-5-phenylisoxazole *(80)* exclusively[36a]. This product apparently results from decomposition of vinyl azide *(79)*, which has both the α-azido- and β-carbonyl groups in a *cis*-configuration.

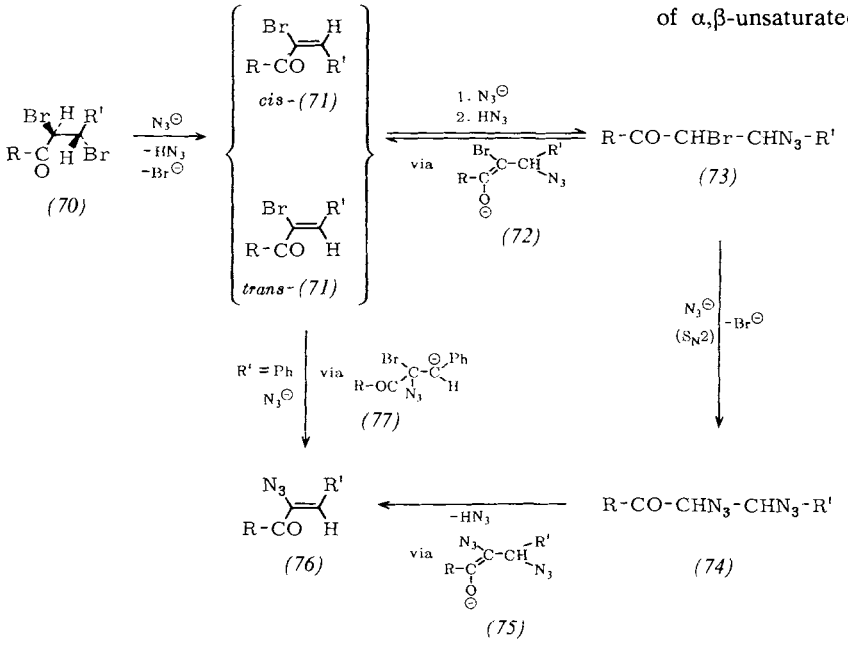


(78) *(79)*



(80)

Unlike in the case of *(70)*, treatment of the dibromides of α,β-unsaturated esters (*e.g.* cinnamate dibromide) with NaN_3 gives a mixture of α- and β-azidovinyl esters[37]. Similar results are obtained with the corresponding iodine azide adducts[37]. Thus *(81)* reacts with one equivalent of NaN_3 in DMF to give, among other products (such as an azirine), both regioisomers *(82)* and

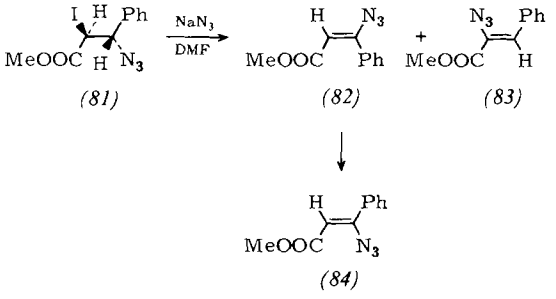


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[36] a) *G. L'abbé*, *M. J. Miller*, and *A. Hassner*, J. Amer. Chem. Soc. in press; b) *G. L'abbé* and *A. Hassner*, J. Org. Chem. in press.

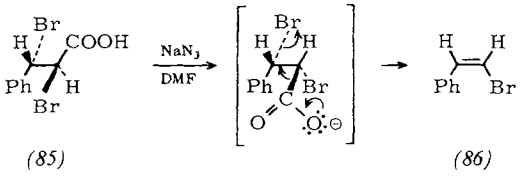
[37] *G. L'abbé*, *M. J. Miller*, and *A. Hassner*, Chem. and Ind. *1970*, 1321.

(83). Typically, when the reaction is carried out with an excess of NaN_3, *(82)* is formed first but isomerizes in the presence of NaN_3 to the more stable *trans* isomer *(84)*. Dehydroiodination of *(81)* with DABCO leads to the β-azidovinyl ester *(82)* exclusively[11b].



(81) *(82)* *(83)* *(84)*

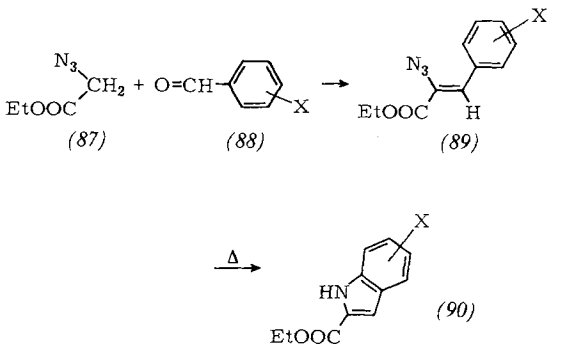
On treatment of the *erythro*-dibromide of cinnamic acid *(85)* with NaN_3, CO_2 evolution occurs and *cis*-β-bromostyrene *(86)* is obtained[37,38].



(85) *(86)*

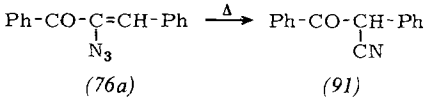
The examples cited above clearly indicate that the three pathways leading to α-azidovinyl ketones in high yields are not convenient for the synthesis of α-azidovinyl esters.

A series of α-azidocinnamates *(89)* were prepared recently[39] by the condensation of azidoacetate *(87)* with substituted benzaldehydes *(88)* in the presence of sodium ethoxide. In order to minimize the well known base-induced decomposition of the α-azidoester *(87)*[40], the reactions must be carried out under well defined conditions of temperature and time. Although the *trans*-configuration of *(89)* is to be expected on thermodynamic grounds, the NMR method proposed for the configurational assignment in these systems has been criticized[36a].



(87) *(88)* *(89)* *(90)*

The use of azidoacetophenone instead of *(87)* led to the synthesis of α-azidochalcones[41] for which a *trans* structure [*(76)*, R = phenyl, R′ = aryl] was proven in other work[36a]. In contrast to the α-azidocinnamates *(89)* which decompose thermally to indoles *(90)*[5b], the α-azidochalcones *(76)* rearrange on thermolysis to α-keto phenylacetonitriles *(91)*[42].



(76a) *(91)*

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Influence of Ligands on the Activity and Specificity of Soluble Transition Metal Catalysts

By G. Henrici-Olivé and S. Olivé[*]

Dedicated to Professor G. V. Schulz on the occasion of his 65th birthday

The reaction of a covalently σ-bonded ligand (alkyl group, hydrogen) with a molecule (olefin, CO) attached to the transition metal by a coordinate bond is the essence of many catalytic processes. The influence of the other ligands in the complex on this reaction is discussed in the present article. Various ways in which the ligands can act, e.g. by electronic effects via the σ and π electron systems of the complex and by steric effects, are first described separately and then illustrated by examples.

1. Introduction

The expression "catalyst tailoring" is commonly used for the processes and efforts whose results and future prospects are to be discussed here.

What is catalyst tailoring? Over the past few decades, soluble transition metal complexes have become extremely important as catalysts for a wide range of reactions. The starting point of this development was probably the discovery by *O. Roelen*[1] in 1938 of the reaction of olefins with carbon monoxide and hydrogen to form aldehydes (the "oxo process" or hydroformylation), which takes place on a soluble cobalt carbonyl complex. Many reactions were subsequently discovered, some of the most important of which are the oxidation of ethylene to acetaldehyde on a palladium complex ("Wacker process")[2], the specific hydrogenation of double bonds on a series of transition metal compounds[3], hydroformylation on rhodium complexes[4], the cyclooligomerization of acetylene[5] and conjugated diolefins[6] on nickel, and the polymerization[7] and oligomerization[8] of olefins on soluble Ziegler-Natta catalysts.

The species that effected the catalysis were at first mostly definite complexes, *e. g. Vaska's*[9] complex $IrCl(CO)[(C_6H_5)_3P]_2$ as a hydrogenation catalyst, *Wilkinson's*[4] $RhH(CO)[(C_6H_5)_3P]_3$ in hydroformylation, and the system $TiCl_4/(CH_3)_2AlCl$ for the oligomerization of ethylene[8]. However, two fields of chemistry that also developed very rapidly at the same time led homogeneous catalysis in a new and extremly interesting direction. On the one hand, transition metals attracted growing interest in preparative coordination chemistry and many new compounds were discovered *(Wilkinson, Chatt, E. O. Fischer,* to name only a few schools), while on the other, important advances in theoretical inorganic chemistry (particularly the ligand field theory) influenced the thinking of catalysis chemists. The result was that more attention was devoted to the significance and the effects of ligands in the transition metal complex. Consequently, the ligands of a complex that was recognized as a catalyst were systematically modified to bring about specific changes both in the rate of the catalyzed reaction and in the final product, in an effort to understand which physical magnitudes (*e.g.* electron density on the metal, orbital energies, steric hindrance) are involved.

We are obviously still at a very early stage in these developments, and we are far from being able to design a homogeneous catalyst in advance for a given purpose (*e.g.* for the addition of molecular nitrogen to olefins). This is a long-term objective, which probably cannot be achieved without a precise knowledge of the kinetic and thermodynamic principles underlying every step of the catalytic reactions. Though research on these principles is being carried out in various places[10–13], procedures in practical catalysis are still semiempirical at best. It nevertheless seems a convenient time to review what has been achieved, one very important reason for this being in order to attract more interest in this young branch of catalysis chemistry, which should have an important future both in scientific and in industrial research.

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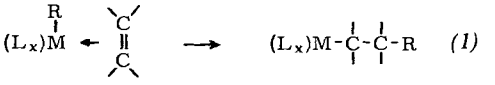
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2. Some Concepts in Homogeneous Catalysis

In most of the known cases of homogeneous catalysis on transition metal complexes, the catalytic reaction takes place between a covalently σ-bonded ligand R (alkyl group, hydrogen) and a substrate molecule (olefin, CO) coordinated to the metal M, the substrate molecule being inserted between the metal and R by a four-center reaction (concerted reaction). This is shown schematically for an olefin in formula (1).



(1)

(L_x) in this formula stands for all the other ligands in the complex. The same process may then be repeated (polymerization, see Sections 4.2 and 4.3), or the catalyst may be restored to its original state by hydrogenolysis or homolysis (cf. Section 4.1). The transition metal itself, the stability of the M–R and M-olefin bonds, and the possibility of influencing these bonds through the other ligands L are therefore of the utmost importance.

2.1. The Transition Metal

Transition metals are characterized in that the $(n-1)$d orbitals have energies similar to those of the ns and np orbitals of the valence shell, and so participate in bond formation. The special symmetry of these d orbitals is responsible for a particular type of bond between the transition metal and the ligand, which does not occur with other metals, and which therefore raises the chemistry of transition metals out of the plane of metal chemistry in general. This is the retrodative π bond (back donation). For symmetry reasons, some of the five d orbitals cannot participate in the normal σ bonds between the metal and the ligands. In an octahedral complex, for example, the orbitals d_{z^2} and $d_{x^2-y^2}$ point in the directions of the six ligands, but the "loops" of maximum electron density in the d_{xy}, d_{xz}, and d_{yz} orbitals lie between these directions. However, these orbitals can overlap with empty antibonding orbitals of suitable symmetry, such as occur in the most important coordinated ligands in catalytically active transition metal complexes, *e. g.* in olefins and CO. This may be illustrated by the well-known Dewar-Chatt-Duncanson model of the metal-olefin bond (Fig. 1).

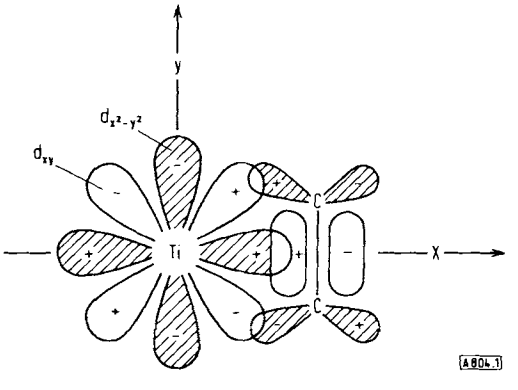


Fig. 1. Coordination of an olefin (ethylene) to a transition metal (titanium); schematic representation of the relevant orbitals in the x–y plane of an octahedral complex. Shaded: empty (acceptor) orbitals.

The bonding π orbital of the olefin, which contains two electrons, has σ symmetry[*] with respect to the axis of the metal olefin bond. It can overlap with an empty dσ orbital of the metal, with formation of a coordinate σ bond. The empty antibonding π* orbital of the olefin has π symmetry[*] with respect to the axis of the bond. If the dπ orbital of the metal that lies in the same plane is occupied, a π bond is also formed. The metal and the olefin can thus form a sort of double bond between them. *Via* the σ bond electron density passes from the olefin to the metal, while *via* the π bond electron density passes from the metal into the antibonding π* orbital of the olefin. Both effects lead to destabilization of the double bond of the olefin, and the distance between the two carbon atoms is increased. This is equivalent to activation of the molecule. The relevance to catalysis is obvious.

The same is true of the coordination of a CO molecule to the metal. A lone pair of electrons on the carbon supplies the σ bond in this case, while the retrodative π bond is formed with the aid of an antibonding π* orbital[14]. In contrast with the case of the olefin, however, the metal, the carbon, and the oxygen lie on the bond axis in this case.



It is not yet possible, in general, to predict which metal is most effective for which catalysis situation. However, certain trends are evident. In the catalysis of polymerization, for example, it is known that catalyst systems containing metals of group VIII of the Periodic System (particularly Co and Ni) are generally favorable for conjugated diolefins, but as far as is known at present they do not polymerize either ethylene or α-olefins. Transition metals situated farther to the left in the Periodic System (Ti, V, Cr) on the other hand, have proved particularly suitable for the polymerization of these compounds.

Soluble complexes of Rh, Ir, Ru, and Co are particularly important in the homogeneous hydrogenation of olefins[3]; Co[1], and Rh[4] have proved particularly suitable for hydroformylation, whereas nickel is the preferred catalyst at present for the cyclooligomerization of butadiene[6].

Some reasons for this "specialization" of the metal complexes will be discussed below.

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[*] σ symmetry is characterized in that the underlying wave functions retain their sign on rotation through 180° about the axis of the bond. In π symmetry, on the other hand, a single change of sign occurs.

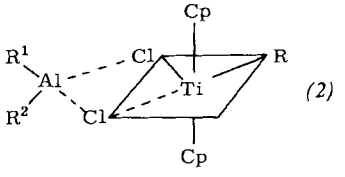
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2.2. Stability of the M–R Bond

The transition metal-carbon bond is generally not very stable. Many organometallic compounds of transition metals can be prepared or isolated only at low temperatures. It was recognized as early as the 1950's, however, that ligands that build up a strong ligand field around the central atom can stabilize alkyl and aryl compounds of the transition metals. With tertiary phosphanes as ligands, it was possible to isolate stable complexes of the type $(PR_3)_2Pt(CH_3)X$ (R = alkyl or aryl; X = halogen) at room temperature[15]. Carbonyl and π-cyclopentadienyl ligands have also been found to have a stabilizing effect[16], and a whole series of very stable organo-transition metal complexes are now known.

It is obvious that excessive stability of the M–R bond is unfavorable to the catalytic activity. The bond must open readily in the course of the reaction and reform with a new R [cf. *(1)*]. It must therefore have just the correct stability.

It has been found that very fine adjustment of the stability of the M–C bond is possible by means of ligands having relatively small differences in their electron donor-acceptor properties. Let us consider as an example the soluble complex *(2)*[17,7], which is formed from Cp_2TiRCl and R^1R^2AlCl, and which catalyzes the pol-



(2)

Cp = π-Cyclopentadienyl, R = Alkyl, R^1, R^2 = Alkyl or Cl.

ymerization of ethylene. It was possible in this case to follow this fine adjustment by direct measurement, since cleavage of the Ti–R bond results in the conversion of a diamagnetic Ti(IV) complex into a paramagnetic Ti(III) complex (measurement of the magnetic susceptibility as a function of time in absence of ethylene). It was found that the destabilization of the Ti–R bond increases in the order $R^1, R^2 = Cl < R^1 = Cl, R^2 = CH_3 < R^1 = Cl, R^2 = C_2H_5 < R^1R^2 = C_2H_5$. The stronger the donor properties of the ligands R^1 and R^2, the stronger is the destabilization of the Ti–C bond.

Though direct measurement is not always as simple as this, the principle of adjusting the stability of the M–R bond by varying the ligands is probably generally applicable. However, the stability of the R–M bond also depends on R itself. Thus for the titanium complex *(2)* with R^1 and R^2 kept constant, the stability varies with R in the order[7]. $CH_3 > CH_2{-}CH_3 > CH_2{-}(CH_2)_n{-}CH_3$.

The same trend has been found in the carbonylation reaction on the manganese complex *(3)*[18]:

$$RMn(CO)_5 + CO \rightarrow RCMn(CO)_5 \quad (3)$$

It was found that the rate of the reaction depends on R, and M–R is most stable (least reactive) for R = methyl, and least stable (highest rate) for R = propyl.

2.3. Coordination of the Substrate

The importance of the coordination on the transition metal to the catalytic process was discussed in connection with Figure 1: the energy barrier to the cleavage and reformation of bonds to the olefin is lowered.

Before an olefin can possibly be coordinated, space must obviously be available in the coordination sphere of the metal. In the case of the titanium/aluminum catalyst *(2)*, the empty coordination site is made available by a change in the symmetry on the central atom on complex formation with the ligand alkylaluminum. The starting substance Cp_2TiRCl is tetrahedral; in this symmetry the metal is saturated coordinately by four ligands. On the approach of the alkylaluminum (*e.g.* $C_2H_5AlCl_2$), the Cl requires a site in the coordination sphere of the Ti in order to form the very stable bridge structure (three-center bonds) between Ti and Al. This forces the central atom to change from tetrahedral to octahedral symmetry[7,17]. (The term "octahedral" here is not quite accurate, since the ligands are not all alike; however, it facilitates discussion and representation by drawings.) We may picture the "vacant site" as being truly vacant or as being occupied by a solvent molecule. However, it is also conceivable *e.g.* that the pentacoordinated complex *(2)* more closely resembles a trigonal bipyramid, and changes into the octahedral structure only on the approach of an olefin.

In other cases the free coordination site is formed by dissociation of a relatively weakly bonded ligand in solution. It is usually assumed that its place is taken by a solvent molecule S, which can be relatively easily displaced by the substrate (olefin). An example is the hydrogenation catalyst chlorotris(triphenylphosphine)-rhodium(I) *(4)*[19,3].

This reaction sequence again involves a change of symmetry, this time from square-planar to octahedral (Scheme 1). Unlike in the complex *(2)*, however, the symmetry change here is associated with a change in the valency of the metal from Rh(I) to Rh(III), and results from the oxidative addition of hydrogen. This process, which is important to the catalytic hydrogenation of olefins, was first observed by *Vaska*[20] in an iridium complex. Square-planar complexes of group VIII metals with the d^8 configuration have a particularly strong tendency to undergo this oxidative addition, in which they change into the d^6 configuration. These complexes are therefore particularly suitable for use as hydrogenation catalysts.

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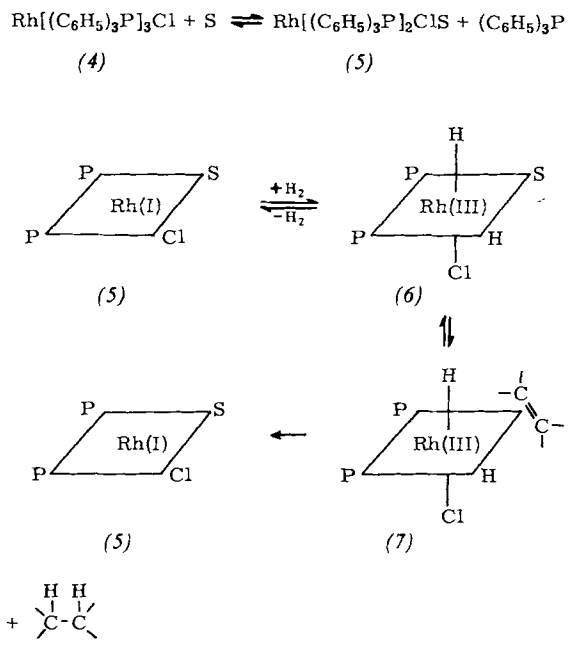
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Scheme 1. S = solvent, P = $(C_6H_5)_3P$

Whether the olefin acts predominantly as a σ donor or as a π acceptor depends on the olefin itself, the metal, and the other ligands. Where the olefin has strong acceptor substituents ($F_2C{=}CF_2$, NC−CH=CH−CN), the electron flux is probably directed predominantly from the metal to the olefin. For ethylene and other simple olefins, spectroscopic studies on iridium complexes[10] and dipole measurements on platinum complexes[21] indicate that the olefins have a basic character toward these metals. Ethylene also acts predominantly as a donor toward the titanium complex *(2)*. This is deduced from the observation that the rate of the reduction Ti(IV) → Ti(III) is increased by the presence of unpolymerizable olefins[7]. The M–R bond is evidently destabilized by the coordination of the olefin (cf. the influence of the donor ligands R^1 and R^2, Section 2.2).

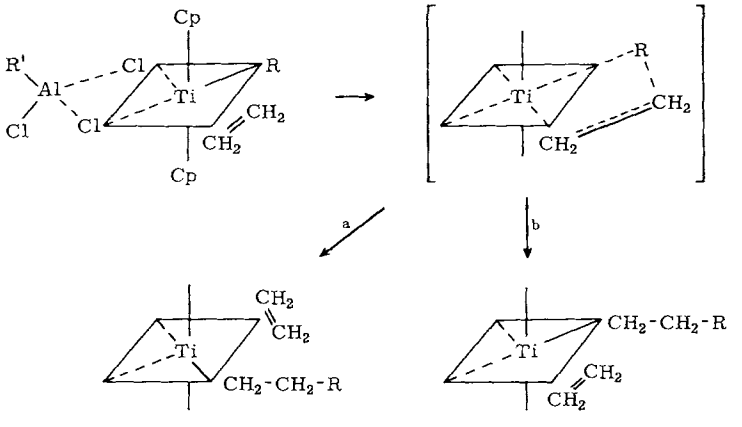
Excessive stability of the coordinate metal-olefin bond is undesirable, for obvious reasons. The absolute values and the relative σ and π bond components must be finely adjusted within narrow limits in order to activate the olefin for catalytic reactions. It must be borne in mind that the requirements imposed on the catalyst in this respect will vary from olefin to olefin. In the kinetic investigation of the S_N1 reaction[22]:

$$CpMn(CO)_2\,(olefin) + L \rightarrow CpMn(CO)_2L + olefin$$

it was found that the coordinate bonding of ethylene to the metal is very much more stable than that of propylene or of 1-pentene. These observations agree *e. g.* with the fact that the rates of polymerization of ethylene, propylene, and 1-butene on the same catalyst[*] are related as 50:5:1[23]. This may be due to steric factors and to the energy of the olefin orbitals that are responsible for the bonding.

2.4. Insertion versus *cis*-Migration

Formula *(1)* was intended to show that the coordinated olefin is "inserted" between M and R. The term "insertion" is used particularly in connection with polymerization reactions. However, it has not yet been possible to establish whether the situation shown results from insertion at the coordination site of the ligand R or from a *cis*-migration of the ligand to the adjacent olefin[24]. Both possibilities are illustrated in Scheme 2 (a: *cis*-migration, b: insertion)[7] for the growth step on the polymerization of ethylene.



Scheme 2

In carbonylation reactions on a managanese catalyst (R = CH_3, coordinated substrate = CO), however, the question seems to have been answered in favor of the *cis*-migration[25,26]. This conclusion is based on the decarbonylation of *trans*-$(CH_3CO)Mn[(C_6H_5)_3P](CO)_4$.

[21] *M. A. Muhs* and *F. T. Weiss*, J. Amer. Chem. Soc. *84*, 4697 (1962).

[22] *R. J. Angelici* and *W. Loewen*, Inorg. Chem. *6*, 682 (1967).

[*] This was in fact a heterogeneous Ziegler-Natta catalyst, but the problem of the coordination of the olefin to the transition metal is the same.

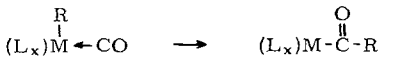
[23] *H. Schnecko*, private communication.

[24] *P. Cossee*, Recl. Trav. Chim. Pays-Bas *85*, 1151 (1966).

[25] *R. J. Mawby, F. Basolo*, and *R. G. Pearson*, J. Amer. Chem. Soc. *86*, 5043 (1964).

[26] *K. Noak* and *F. Calderazzo*, J. Organometal. Chem. *10*, 101 (1967).

According to the law of microscopic reversibility, it is to be expected that the same reaction path will be followed (but in the opposite direction) as in the carbonylation, in which CO is "inserted" between the metal and an alkyl group.



Owing to the phosphane ligand in the *trans* position, the products of decarbonylation by the two paths should be stereoisomers. The fact that *cis*-$CH_3Mn[(C_6H_5)_3P](CO)_4$ is formed shows that the probable mechanism is *cis*-migration, and not insertion.

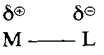
3. Influences of the Ligands L

The ligands L [cf. *(1)*] may be ions (Cl^-, CN^-, H^-, *etc.*) or neutral molecules (phosphanes, phosphites, amines, CO, NO, *etc.*). A number of concepts have been used to interpret the influence of such ligands on the stability of the M–R and M–olefin bonds, and hence on the catalytic activity. These include the σ-donor ability or basicity of the ligands[6,7,27], the π-acceptor strength of the ligands[13], the *trans* effect[28], the inductive effect[29] and the resonance effect[30], the electron density on the metal[13,7], and the influence on the energies of the orbitals[15,17,31]. These concepts stem in part from different theories of chemical bonding (the valence bond theory, the MO theory, the ligand field theory), but they are all basically descriptions of the same thing: a change in the electronic structure, *i. e.* a decrease in the electron density in certain regions of the complex, an increase in others, and a consequent change in the bonding.

With few exceptions[7,27,29], however, no clear relationships have yet been discovered between continuously variable properties of a ligand (*e. g.* the basicity of phosphanes[27] and phosphites[29] or alkyl ligands[7]) and catalytic activity. This is probably because the catalytic processes are mostly complicated reaction sequences, in which the activation of different steps may place entirely different requirements on the ligands. To destabilize the M–R bond the σ-electron system must be influenced, while the activation of the coordinated substrate (retrodative π bonding) may occur preferentially *via* the π-electron system; a ligand L must frequently be dissociated in order to make a coordination site available, and the important factor then is strength of the M–L bond itself. There is therefore no reason to expect a simple relationship between electronic structure and reactivity. An attempt will nevertheless be made here to discuss the various factors separately.

3.1. Effects Acting *via* the σ-Electron System

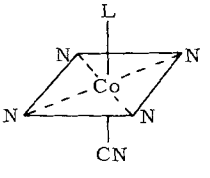
Let us first consider an undoubtedly greatly simplified electrostatic picture in which the central transition metal ion is positively charged[*], and all the bonds between the metal and the ligands, including R and olefin, must be regarded as more or less polar:



If a ligand L^1 is now replaced by another ligand L^2 that is a better electron donor (*i. e.* is more basic, or has a lower electron affinity, or however one may express it) than L^1, the positive charge on the metal is reduced, with the result that the bonding between the metal and all the other ligands is weakened. However, this weakening generally affects only the relatively unstable M–R bond sufficiently, so that it consequently becomes reactive.

A similar result regarding the weakening of the σ bonding to all the other ligands follows from a MO calculation (extended Hückel MO) on *trans* and *cis* effects in square-planar Pt(II) complexes of the type $PtCl_2(L)(NH_3)$[32]. The more strongly σ bonding the ligand L ($H > PH_3 > CH_3 > H_2S > Cl > NH_3 > H_2O$), the lower is the electron density in the overlap region of the corresponding atomic orbitals between the metal and all the other ligands, *i.e.* the weaker are these bonds. It is interesting to note that it was found that contrary to general belief, the *cis* bond is weakened almost as much as the *trans* bond. Experimental evidence of this based on IR spectroscopic studies (bond force constants) has already been reported[33].

IR spectroscopic studies on cobalt(III) corrinoids *(8)*, which are complexes related to vitamin B_{12}, show that theses effects are not confined to square-planar complexes, as the cobalt in these complexes is hexacoordinated[34,35].



(8)

The four N atoms shown represent the corrin system, and L is the ligand to be varied. The bonding to all the other ligands becomes weaker with increasing donor strength of L ($CH_3–CH_2 > CH_3 > CH_2 = CH > CH \equiv C > CN > OH$); the ligand that is most strongly affected is the CN group in the *trans* position.

The σ-donor strengths (basicities) of phosphanes and phosphites *etc.* decrease in the following or-

[27] *C. O'Connor* and *G. Wilkinson*, Tetrahedron Lett. *1969*, 1375.

[28] *J. A. Osborn, F. H. Jardine, J. F. Young*, and *G. Wilkinson*, J. Chem. Soc. *A 1966*, 1711.

[29] *W. R. Moser*, J. Amer. Chem. Soc. *91*, 1135, 1141 (1969).

[30] *K. G. Claus* and *J. V. Rund*, J. Catalysis, *15*, 304 (1969).

[31] *P. Cossee*, J. Catalysis *3*, 80 (1964).

[32] *S. S. Zumdahl* and *R. S. Drago*, J. Amer. Chem. Soc. *90*, 6669 (1968).

[*] This is valid even for complexes that have a formally zero-valent or negatively charged central atom, since the extra electrons are largely delocalized over the ligands.

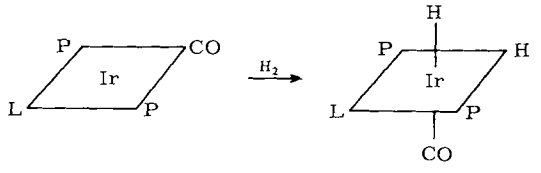
[33] *K. Nakamoto, P. J. McCarthy, J. Fujita, R. A. Condrate*, and *G. T. Behnke*, Inorg. Chem. *4*, 36 (1965).

[34] *R. A. Firth, H. A. O. Hill, J. M. Pratt, R. G. Thorp*, and *R. J. P. Williams*, J. Chem. Soc. *A 1968*, 2428.

[35] *H. A. O. Hill, J. M. Pratt*, and *R. J. P. Williams*, Discuss. Faraday Soc. *47*, 165 (1969).

ders[27,29,36,37]: $(C_2H_5)_3P > (CH_3)_3P > (C_2H_5)_2P(C_6H_5) > (C_2H_5)P(C_6H_5)_2 > (C_6H_5)_3P$; $R_3P > (RO)_3P$; $(CH_3OC_6H_4O)_3P > (C_6H_5O)_3P > ClC_6H_4O)_3P$; $R_3P > R_3As > R_3Sb$.

Another possible influence of a ligand L *via* the σ-electron system should be mentioned. This concerns the oxidative addition of H_2 to square-planar complexes, a reaction that plays an important part in many catalytic hydrogenations (cf. Scheme 1). It was found that for the compound *trans*-$IrL(CO)[(C_6H_5)_3P]_2$ (L = halogen ligand), the rate of additions decreases considerably in the order I > Br > Cl[12].



The electronegativities of the halogen atoms decrease in the reverse order; thus iodine attracts the σ electrons less than the other two halogens, *i. e.* the central atom is less positive when L = I. According to the above discussion, this means that all the other ligands are less strongly bound than in the complexes with L = Br or L= Cl. It may be imagined that this weaker bonding will facilitate the "flip" from the square-planar to the octahedral structure. (Since the two H atoms are added in the *cis* position, one ligand must move out of the x–y plane and enter into bonding with the d_{z^2} orbital.)

3.2. Effects Acting *via* the π-Electron System

In the case of ligands that have orbitals of the appropriate symmetry available (antibonding π*-orbitals in olefins and CO, d orbitals of the phosphorus in phosphanes, *etc.*), the influence of the π electrons is superimposed on the action *via* the σ-electron system. A ligand that can act as a π acceptor can withdraw electrons from the π bonds to other ligands; the dπ orbitals of the metal act as a "conductor" for the electrons. This is illustrated schematically in Figure 2 for a metal complex with a CO and a phophorus ligand. The possible effect on the metal-CO or metal-olefin bond in catalytic processes is obvious.

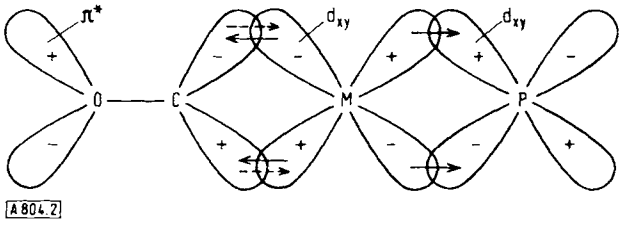


Fig. 2. Retrodative π bond between metal and CO on the one hand and between metal and phosphane on the other. The π bond to the CO is weakened by the presence of the phosphane (σ orbitals not shown).

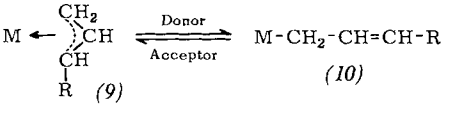
This effect is again determined experimentally by IR spectroscopy. In carbonyl complexes, for example, the CO stretching frequency ν_{CO} depends on how much electron density passes into the antibonding π* orbital of the CO by retrodative π bonding from the metal to the CO; the greater this quantity, the weaker is the bond between C and O, and the lower is ν_{CO}[*]. If electron density is withdrawn from π*(CO) by a π acceptor at another point in the complex, ν_{CO} is increased. NO can be used in a similar manner as a "diagnostic ligand". By investigations on complexes of the type $ML(CO)X_n$ or $ML(NO)X_n$ in which the metal (M) and the other ligands (X_n) are kept constant while L is varied, it is possible to arrange the ligands L in order of their π-acceptor strength[13,38-40]. The following series are obtained: NO ≈ CO > PF_3 > PCl_3 > $PCl_2C_6H_5$ > $PCl(C_6H_5)_2$ > $P(C_6H_5)_3$ > $P(C_2H_5)_3$; $PCl_2(OC_2H_5)$ > $P(OC_6H_5)_3$ > $P(OC_2H_5)_3 \approx P(OCH_3)_3 > P(CH_3)_3 > P(C_2H_5)_3$; $PR_3 \approx AsR_3 \approx SbR_3$.

Halide ions have no appreciable influence on ν_{CO}. They do not appear to act either as π acceptors or as π donors[38]. Their influence on catalytic reactions is probably due to effect acting via the σ-electron systems.

3.3. "σ−π Equilibrium" of Carbon Ligands

The delocalized π-electron systems of allyl ligands allows them to form bonds with the metal of a type that resembles those formed by olefins[41]. A σ bond is formed by the occupied bonding allyl orbital and an empty σ orbital of the metal, and the π bonding takes place between a dπ orbital of the metal and the half-occupied nonbonding allyl MO. However, the π-bonding is less important than *e. g.* in the case of ethylene. This is shown by the fact that the plane of the three carbon atoms of the allyl group forms an angle of more than 100° with the plane defined by the metal and the other ligands[42].

Under the influence of basic ligands (σ donors, *e. g.* phosphanes), this configuration can change with formation of a localized σ bond between the metal and the carbon *(10)*[6,43], whereas the "π complex" *(9)* is favored in the presence of acceptor ligands (*e.g.* Cl).



(9) *(10)*

Processes of this type often occur in reactions involving conjugated diolefins, *e. g.* in the dimerization or

[*] However, the stretching frequency ν_{CO} is also affected *via* the σ bonding. The contributions of the two effects to the measured result is not yet certain (see [38] and literature cited there).

[36] *L. Maier*, Progr. Inorg. Chem. *5*, 27 (1963).

[37] *R. P. Stewart* and *P. M. Treichel*, Inorg. Chem. *7*, 1942 (1968).

[38] *C. A. Tolman*, J. Amer. Chem. Soc. *92*, 2953 (1970).

[39] *W. D. Horrocks* and *R. C. Taylor*, Inorg. Chem. *2*, 723 (1963).

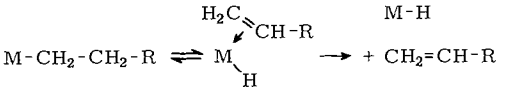
[40] *J. Mašek*, Inorg. Chim. Acta, Reviews, *3*, 99 (1969).

[41] See *e. g. G. Henrici-Olivé* and *S. Olivé:* Polymerisation, Katalyse-Kinetik-Mechanismen. Verlag Chemie, Weinheim 1969, p. 180.

[42] *S. F. A. Kettle* and *R. Mason*, J. Organometal. Chem. *5*, 573 (1966).

[43] *W. Brenner, P. Heimbach, H. Hey, E. W. Müller*, and *G. Wilke*, Liebigs Ann. Chem. *727*, 161 (1969).

cyclooligomerization of butadiene (cf. Section 4.4) or its codimerization with ethylene[44]. A similar equilibrium probably also occurs in the polymerization or oligomerization of ethylene, *e.g.* on Ti(IV) catalysts (cf. Section 4.2).



The relative frequency of this β-hydrogen transfer depends on the electron affinity of the metal, *i. e.* on the donor-acceptor behavior of the other ligands in the complex. If the electron affinity of the Ti is reduced (donor ligands), the hydrogen transfer occurs less frequently, *i. e.* the polymer molecules become longer.

To understand these processes, one must bear in mind that the σ-bonded carbon ligand supplies only one electron to the complex, whereas the π-allyl group or the combination of π-olefin and hydrogen ligand contributes three.

3.4. Bond Strength of the Ligand L

Reactions in which the vacant coordination site must be formed by dissociation of a ligand also depend on the strength with which this ligand is bonded.

The bonding strength for a series of ligands in octahedral chromium complexes has been estimated by measurement of the rate of replacement of L by CO[45]:

$$(phen)Cr(CO)_3L + CO \rightarrow (phen)Cr(CO)_4 + L$$

(phen = *o*-phenanthroline, a bidentate ligand). Since this process may be assumed to proceed by a dissociative mechanismen, the rate may be taken, to a first approximation, as a measure of the bond strength. The stability was found to decrease with L in the order $P(n\text{-}C_4H_9)_3 > P(OC_2H_5)_3 > CO > P(OC_6H_5)_3 > P(C_6H_5)_3 > PH_2(C_6H_5)$. A similar order has been found for tungsten complexes[46].

The order of the ligands varies in the same manner as the basicity rather than as the π-acceptor strength. The strength of the bond in this case thus appears to depend mainly on the σ-bonding. In an octahedral ruthenium complex in which the ligand L is situated *trans* to a hydrogen ligand, however, it was found that $L = (RO)_3P$ is more strongly bonded than $L = R_3P$[47]. The strong σ donor H evidently weakens the *trans* σ bond (cf. Section 3.1), to such a degree that the retrodative π bond from the metal to the phosphorus becomes the deciding factor for this bond.

3.5. Steric Effects

Bulky ligands can influence a catalytic process by allowing coordinative addition of the substrate only in a certain orientation; the result may be stereospecific catalysis. A typical example is the syndiotactic polymerization of propene on soluble vanadium catalysts at low temperatures[48]; chlorine ligands and the methyl group of the last propene molecule incorporated into the growing chain form a sort of rigid frame (matrix), which predetermines the direction of addition of the monomer. (Stereospecific polymerization on heterogeneous catalysts is based on the same principle.) This matrix formation on transition metal catalysts can even be used for the synthesis of optically active substances[49,50]. Thus optically active ligands such as (+)methylphenylpropylphosphane or (+)-phenylethylformamide have been used in rhodium complexes for the hydrogenation of α-ethylstyrene to (+)-2-phenylbutane (7–8% optical yield) and of methyl 3-phenyl-2-butenoate to optically active methyl 3-phenylbutyrate (50% optical yield).

The direction of a catalytic reaction can sometimes be changed by blockage of coordination sites. For example, cyclooctatetraene is formed from acetylene on Ni(II) chelates [*e.g.* bis(2-alkyliminomethylphenolato)nickel(II)][5,51]. It is assumed that the two chelating ligands can be displaced by the acetylene so that they each occupy only one coordination site. Four acetylene molecules then complete an octahedral structure and assume a steric arrangement that favors the formation of cyclooctatetraene. If a basic ligand that is too strongly bound to be displaced by acetylene [$P(C_6H_5)_3$, in a ratio of 1 : 1 with respect to the nickel compound] is introduced into the system, one site is blocked and only three acetylene molecules can now be added. Instead of cyclooctatetraene, therefore, the main product is benzene[51].

4. Examples of the Specific Modification of the Catalytic Activity

4.1. Hydrogenation of Olefins

Wilkinson et al.[19,27] studied the effect of varying the ligand in catalysts of the type $(R_3El)_3RhX$ on the rate of hydrogenation of olefins. The components that were varied were El(P, As, Sb), R(alkyl and aryl groups), and X(Cl, Br, I). Kinetic measurements showed that the reaction mechanism is probably as indicated in Scheme 1 (Section 2.3), *i. e.* dissociation of a ligand R_3El and replacement by a solvent molecule S, oxidative addition of H_2, replacement of S by the olefin, and transfer of the hydrogen to the olefin. A competing reaction in which S is replaced by olefin before the oxidative addition of H_2 does not lead to hydrogenation of the olefin. According to the views discussed here, the reason for this may be that the σ-donor strength of the olefin is not enough to ensure the "flip" into the octahedral complex (cf. Section 3.1).

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[44] *A. Miyake, G. Hata, M. Iwamoto,* and *S. Yuguchi,* 7. World Petroleum Congress, P. D. No. 22(3), Mexico 1967.

[45] *G. R. Dobson* and *L. A. Smith,* Inorg. Chem. *9,* 1001 (1970).

[46] *R. J. Angelici* and *C. M. Ingemanson,* Inorg. Chem. *8,* 83 (1969).

[47] *P. G. Douglas* and *B. L. Shaw,* J. Chem. Soc. *A 1970,* 1556.

[48] *J. Boor Jr.* and *E. A. Youngman,* J. Polymer Sci. *A-1, 4,* 1861 (1966).

[49] *L. Horner, H. Büthe,* and *H. Siegel,* Tetrahedron Lett. *1968,* 4023.

[50] *P. Abley* and *F. J. McQuillin,* Chem. Commun. *1969,* 477.

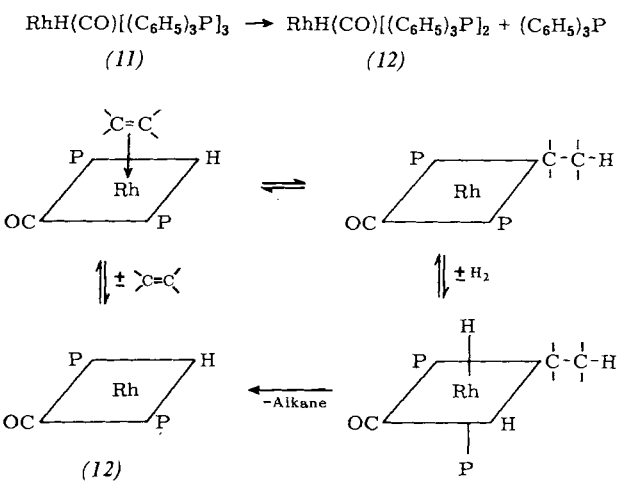
[51] *G. N. Schrauzer,* Angew. Chem. *76,* 28 (1964); Angew. Chem. internat. Edit. *3,* 185 (1964).

In the series with El=P, the activity increased with variation of R in the order *p*-Cl-C_6H_4 (1.6) < *p*-F-C_6H_4 (5.8) < C_6H_5 (40) < *p*-CH_3-C_6H_4 (85) < *p*-CH_3O-C_6H_4 (100). The figures in parentheses are the relative rates of hydrogenation of cyclohexene. The basicity of the phosphanes increases in the same order. It may be assumed that the accelerating effect is due to greater ease of the oxidative addition of H_2 and/or to weakening of the M–H and M–olefin σ bonds in the complex *(7)*, as described in Section 3.1.

A similar trend is shown by the observation that the rate is greatly reduced on replacement of $(C_6H_5)_3P$ by $(C_6H_5)_3As$, and becomes practically zero with $(C_6H_5)_3Sb$. As was mentioned in Section 3.1, the basicity (σ-donor strength) decreases in the same order. This picture is also in agreement with the discovery that when X is varied, the rate decreases in the order I > Br > Cl.

The σ-donor argument, however, cannot be applied in the same way to the series $(C_6H_5)_3P$ (36) ≈ $(C_6H_5)_2PC_2H_5$ (37) > $C_6H_5P(C_2H_5)_2$ (3.4) > $P(C_2H_5)_3$ (1). (Once again relative hydrogenation rates are given.) Here the reactivity and basicity of the phosphane obviously do not run parallel. We recall however that alkylphosphanes are more firmly bound to the metal than are arylphosphanes (Section 3.4). Replacement of a phosphane ligand by solvent with formation of the complex *(5)* thus appears to be the rate-determining step. This is also indicated by the fact that an excess of phosphane leads to a reduction in the rate[19]. Presumably the bond strength does not differ substantially within the series of *p*-substituted phenylphosphanes mentioned above, so that in this case the inductive effect of the *p*-substituents of the phosphane ligands remaining in the complex predominates.

An interesting ligand effect is also found on comparison of the hydrogenation catalysts $RhCl[(C_6H_5)_3P]_3$ *(4)* and $RhH(CO)[(C_6H_5)_3P]_3$ *(11)*[52]. The rates of hydrogenation under comparable conditions are related as 2:1 for the two catalysts, but complex *(11)* is specific for 1-olefins, whereas complex *(4)* hydrogenates different positional isomers at approximately the same rate. *Wilkinson et al.*[52] found that *(11)* acts by a different reaction mechanism. After the dissociation of a phosphane ligand, olefin is first coordinated and is then inserted into the metal-H bond (see Scheme 3). According to the workers who studied this system, this is possible only for 1-olefins, on steric grounds. It should also be remembered, however, that the strong π-acceptor ligand CO makes the coordination of the olefin difficult (weakening of the retrodative π bonding), and allows it to occur only under the most favorable conditions (1-olefins). The CO ligand is probably also responsible for the decrease in the rate.

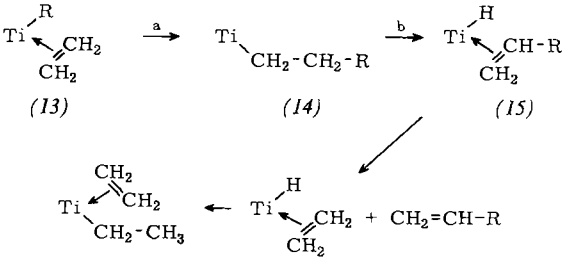


Scheme 3

Finally, mention should be made of a ligand effect in hydrogenation with a Ziegler-Natta system[53]. The combination $CoCl_2$ + AlR_3 hydrogenates both 1-olefins and conjugated diolefins. If a phosphane or phosphite is added, conjugated diolefins are hydrogenated preferentially. The explanation of this effect is that only the dienes are able to displace the phosphane from the complex and so to approach the catalytically active species.

4.2. Oligomerization of Ethylene (1-Olefins)

The influence of ligands is clearly shown by a comparison of the two Ziegler-Natta systems $Cp_2TiRCl/RAlCl_2$ (Cp = cyclopentadienyl, R = alkyl)[7,17] and $TiRCl_3/RAlCl_2$[8]. Whereas solid polyethylene is obtained with the first of these catalysts, the second gives liquid oligoethylenes consisting mainly of 2-ethyl-1-olefins (vinylidene end groups). However, a certain influence of the solvent (toluene or CH_2Cl_2) and the temperature (0 and −70 °C) must be taken into account.



Scheme 4. For the sake of clarity, only the processes at the two coordination sites of the titanium in which we are interested are shown.

The great difference in product composition that is achieved by modification of only two ligands on the titanium led to the hope that by systematic variation of the ligands (with simultaneous temperature control), it would be possible to reach a region yielding linear 1-olefins in a molecular weight range that would be of interest for many applications (C_6–C_{40})[54]. Two opposing tendencies were observed. On the one hand, the chain length depends on the electron donor-acceptor properties of the

[52] *C. O'Connor* and *G. Wilkinson*, J. Chem. Soc. *A 1968*, 2665.

[53] *Y. Tajima* and *E. Kunioka*, J. Catalysis *11*, 83 (1968).

[54] *G. Henrici-Olivé* and *S. Olivé*, Angew. Chem. *82*, 255 (1970); Angew. Chem. internat. Edit. *9*, 243 (1970).

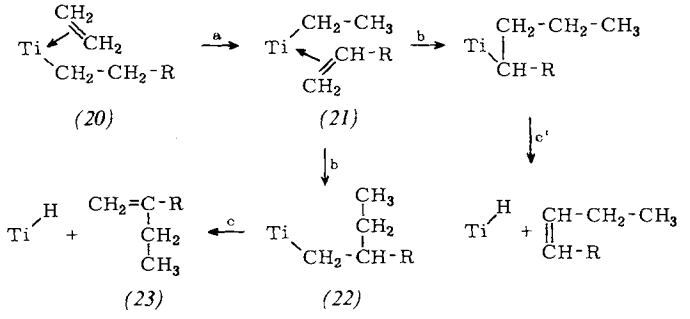
ligands. The greater the electron affinity of the titanium, the more important does the β-hydrogen transfer (reaction b, Scheme 4) become in relation to the chain growth reaction (reaction a), *i. e.* the lower does the molecular weight become (cf. Section 3.3). This tendency is clearly shown by Table 1.

Table 1. Dependence of the molecular weight of the ethylene polymer obtained on the ligands at the titanium. Al component: $C_2H_5AlCl_2$; Al/Ti = 5; solvent: benzene; $T = 5°C$; $p_{C_2H_4} = 1$ atm.

System	Ti component	Oligomers [a] (%)	Polymers (%)
(16)	$(C_2H_5O)_4Ti$	31	69
(17)	$(C_2H_5O)_3TiCl$	56	44
(18)	$(C_2H_5O)TiCl_3$	77	23
(19)	$TiCl_4$	92	8

[a] The oligomer is taken to be the part that is soluble in benzene at room temperature.

On the other hand, a high electron affinity of the titanium also allows an undesirable side reaction to take place; this reaction is indicated by the reaction sequence *(20)* to *(23)* in Scheme 5. The β-hydrogen



Scheme 5

transfer with conversion of the Ti–C σ bond into the π complex (Scheme 4, reaction b) occurs not only when the adjacent coordination site is vacant, but also when it carries a monomer. The normal growth is then replaced by transfer of hydrogen to the ethylene (Scheme 5, reaction a), and the growth step (b or b') leads to an ethyl or propyl branch. If this is again followed immediately by β–H transfer (c or c') a vinylidene end group or an inner double bond is formed. With the system that favors low molecular weight [*(19)* in Table 1], the content of 1-olefins is only about 5%, whereas with the system *(16)*, the oligomeric part consists mainly of 1-olefins at comparable conversions.

By lowering the temperature, however, the average molecular weight can be reduced without deterioration of the ratio of the principal reaction to the undesirable side reaction (Scheme 4/Scheme 5). [Since the polymerization rate is reduced to approximately the same degree, the effect is probably due to a decrease in the rate of the normal growth step *(13)* → *(14)*.] Thus it was finally possible, with the system *(17)* at −20 °C, to obtain a product containing 75% of 1-olefins having molecular weights in the range ≤ 300[54].

4.3. Oligomerization of Propene

Propene undergoes cationic oligomerization in the presence of Lewis or Brönsted acids to give oily to waxy oligopropene[55,56]. However, the growing chain end (carbonium ion) also reacts with the tertiary hydrogen atoms of the polymer chain (hydride transfer), with the result that highly branched products are formed.

The Ziegler-Natta systems listed in Table 2 were tested in an attempt to prepare unbranched polypropene having a relatively low molecular weight[57]. The object was to shift the place of polymerization from the solution (polymerization of free cations) to a coordination site in a titanium complex. In coordinative polymerization on a transition metal center[17], no free cations occur; on the contrary, the growing chain end carries a certain negative charge because of the polarization of the metal-carbon bond:

$$\overset{\delta\oplus}{Ti}\ldots\ \overset{\delta\ominus}{CH_2}\text{-}CH(CH_3)\text{-}R$$

The undesirable chain branching can therefore be suppressed. The result of these efforts was checked by IR spectroscopy. A band at 1155 cm^{-1} is characteristic of the grouping $-CH_2-CH(CH_3)-CH_2$[58]. Since the tertiary hydrogen is lost on branching, this band provides a measure of linearly incorporated propene (column 8 in Table 2).

The linearity of the product increases, *i.e.* the cationic initiation is suppressed, with the depression of the Lewis-acid character (decrease in the electron affinity of the

Table 2. Effect of ligands on the linearity of oligopropene [57] [Ti] = 20.10^{-3} mole/l; $T = 5°C$; solvent: benzene.

System	Ti component	Al component	Al/Ti	$p_{C_3H_6}$ (atm.)	Propene uptake (mole $l^{-1}h^{-1}$)	$\bar{M}_n$[a]	Linear growth (%)
(19)	$TiCl_4$	$C_2H_5AlCl_2$	5	1	2.2	516	28
(17)	$(C_2H_5O)_3TiCl$	$C_2H_5AlCl_2$	5	1	1.0	340	49
(16)	$(C_2H_5O)_4Ti$	$C_2H_5AlCl_2$	5	1	0.12	432	87
(24)	$TiCl_4$	$(C_2H_5)_2AlCl$	2	1	2.2	555	70
(25)	$TiCl_4$	$(C_2H_5)_2AlCl$	2	5	4.5	770	68
(26)	$(C_2H_5O)TiCl_3$	$(C_2H_5)_2AlCl$	1.3	5	2.2	1100	94

[a] Number average molecular weight.

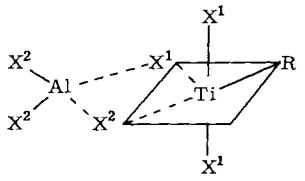
[55] *E. H. Immergut, G. Kollmann,* and *A. Malatesta,* J. Polymer Sci. *51,* S 57 (1961).

[56] *C. M. Fontana,* J. Phys. Chem. *63,* 1167 (1959).

[57] *G. Henrici-Olivé* and *S. Olivé,* J. Polymer Sci. *B–8,* 205 (1970).

[58] *G. Natta, A. Valvassori, F. Ciampelli,* and *G. Mazzanti,* J. Polymer Sci. *A–3,* 1 (1965).

titanium) by donor ligands. It is assumed from analogy that the titanium complex that allows the coordinative polymerization has a structure similar to that of the octahedral complex *(2)* (Section 2.2).



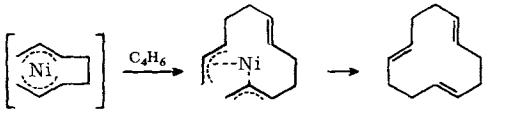
R = C_2H_5 or growing chains, X^1 = Cl or C_2H_5O, X^2 = Cl or C_2H_5.

It can bee seen in Table 2 that ethyl ligands on the Al exert a stronger influence *via* the bridge bond than C_2H_5O ligands attached directly to the titanium [cf. *e.g.* systems *(17)*, *(19)*, and *(24)*]. The reaction rate is considerably slower in coordinative polymerization than in polymerization *via* free cations [cf. systems *(16)*, *(17)*, and *(19)*]. This can be partly balanced by the use of higher propylene pressures [systems *(24)* and *25)*], but the molecular weight then also increases. Almost ideally linear growth was achieved with the system *(26)*.

4.4. Cyclooligomerization of Butadiene

The catalytic cyclotrimerization of butadiene to form cyclododecatriene (CDT) *(29)*[6,59,60] and the cyclodimerization to form cyclooctadiene (COD) *(30)*[43] on Ni(0) catalysts were discovered by *Wilke et al.*

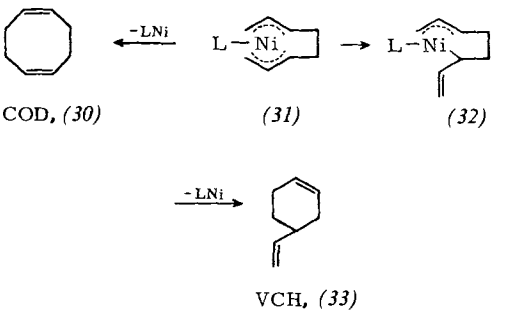
Reduction of soluble nickel salts with alkylaluminum in presence of butadiene yields atomic nickel, which is held in solution by ligands formed from butadiene. The complex *(27)*, in which two butadiene molecules linked to form a C_8 chain are bonded to a nickel atom by two π-allyl groups, is assumed to occur as an intermediate. If no other ligands are present in the system, *(27)* takes up a further molecule of butadiene to form *(28)*. The trimer is displaced from the complex as cyclododecatriene *(29)* by fresh butadiene molecules, with formation of *(27)* once more.



(27) *(28)* CDT *(29)*

Scheme 6

One coordination site on the nickel can be blocked by addition of a ligand L (triarylphosphane or triaryl phosphite) in a ratio of 1:1 with respect to the nickel. Dimer is then displaced from the intermediate *(31)* (which can be isolated at low temperatures) by further butadiene either as cyclooctadiene *(30)* or as vinylcyclohexene (VCH) *(33)*. Some cyclododecatriene *(29)* ist always also formed.



COD, *(30)* *(31)* *(32)*

VCH, *(33)*

The ratio of the yields of *(30)*, *(29)*, and *(33)* is strongly dependent on the electron donor properties of the ligand L, as is shown by Table 3.

Table 3. Cyclooligomerization of butadiene; dependence of the composition of the reaction product on the ligand L. T = 80 °C; normal pressure, 3 hours (after [43]).

L	COD(%)	VCH(%)	CDT(%)	$>C_{12}$(%)
$(C_6H_5)_3As$	17	5.8	60	14
$(C_6H_5)_3P$	64	27	6	2.8
$(C_6H_{11})_3P$ [a]	41	40	14	4.8
$(C_6H_4O)_3P$	81	7.4	9.2	2.3
$(o\text{-}CH_3\text{-}C_6H_4O)_3P$	92	5.7	1.4	0.6
$(o\text{-}C_6H_5\text{-}C_6H_4O)_3P$	96	3.1	0.2	0.2

[a] Tricyclohexylphosphane.

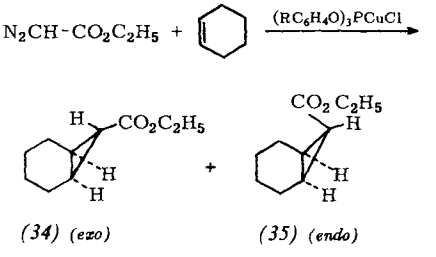
Electron acceptors such as triaryl phosphites stabilize the nickel-bis(π-allyl) complex *(31)*, which preferentially forms cyclooctadiene. Electron donors (alkylphosphane > arylphosphane), on the other hand, apparently cause the conversion of a π-allyl into a σ-allyl group [complex *(32)*], with the result that the linkage of C–1 with C–6 to form vinylcyclohexene *(33)* is favored (cf. Section 3.3).

o-Substituted triphenyl phosphites increase the yield of cyclooctadiene. Since the electronic properties of the *o*-substituent are of no appreciable importance, this is assumed to be due to a steric effect.

In the presence of triphenylarsine, however, the reaction proceeds predominantly as shown in Scheme 6, in agreement with the fact that $(C_6H_5)_3As$, stands at the lower end both of the series of σ donors (Section 3.1) and of the series of π acceptors (Section 3.2), so that no appreciable interaction with the metal is to be expected.

4.5. Addition of Diazoalkanes to Olefins

The addition of ethyl diazoacetate to cyclohexene with chloro(triaryl phosphite)copper(I) as the catalyst has been studied by *Moser*[29]. The reaction proceeds in accordance with Scheme 7.



(34) (exo) *(35) (endo)*

Scheme 7

[59] *H. Breil, P. Heimbach, M. Kröner, H. Müller,* and *G. Wilke,* Makromol. Chem. *69*, 18 (1963).

[60] *B. Bogdanović, P. Heimbach, M. Kröner,* and *G. Wilke,* Liebigs Ann. Chem. *727*, 143 (1969).

The two isomeric cyclopropane derivatives *(34)* and *(35)* are formed in a yield of 30–70% together with diethyl fumarate and diethyl maleate. The ratio of *exo* compound to *endo* compound depends on the substituent R in the phosphite ligand, and decreases as R varies in the order o-CH_3 > m-CH_3 > p-H > p-Cl > p-CH_3CO. This result is interpreted by *Moser* as follows. The better the acceptor properties of the phosphite ligand on the copper, the greater is the positive charge on the metal, and the stronger, therefore, is the bonding with all the other ligands. The decrease in the bond lengths leads to steric hindrance between the reactant (coordinated cyclohexene) and the phosphite ligand. It is plausible on the basis of a model of the transition state, that this will favor the formation of the *endo* form.

For the *o*- and *m*-substituted phenyl phosphites, a linear relation exists between the ratio log*(exo/endo)* and the Hammett σ values for the substituents R. This indicates that the effects observed are purely electronic in origin. Nevertheless, they ultimately act *via* the steric hindrance of one of the two possible transition states. The author speaks of stereo-electronic effect. In the case of *o*-substitution, the values found for *(exo/endo)* are lower than those expected from the Hammett lines. This purely steric effect shows again that steric hindrance places the *exo* form *(34)* at a disadvantage in relation to the *endo* form *(35)*.

5. Conclusion

The number of systematic studies that have been carried out on the influence of the ligands on the catalytic activity of a transition metal catalyst is still relatively small. As long as a broad experimental basis is lacking, one cannot entirely rule out the possibility of occasional misinterpretations. In this sense, the present review is intended mainly to stimulate interest. We would be content if it led to the initiation of a few systematic studies that might help to deepen our understanding of these relationships, which are so important to the entire field of catalysis on transition metals.

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Radical Anion Intermediates in Organic Chemistry[**]

By N. L. Holy and J. D. Marcum[*]

Radical anions are reactive intermediates in a variety of organic reactions. They make possible several unique synthetic conversions and provide an opportunity for investigating structural relationships. Examples of such reactions are given and current mechanistic views are discussed.

1. Introduction

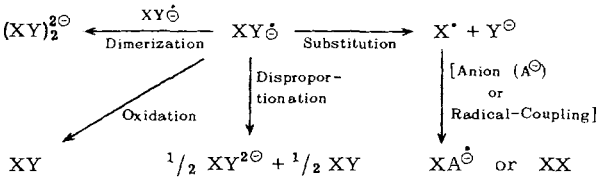
A radical anion results from chemical, electrolytic, or photolytic reduction:

$$XY + e^{\ominus} \rightarrow XY^{\dot{\ominus}}$$

The minus sign appearing in this symbol indicates the presence of a negative charge characteristic of an ion, and the dot indicates that the new species possesses an odd number of electrons and therefore a radical nature.

The most thoroughly studied electron-accepting systems are those of aromatic compounds; then alkyl halides, alkenes, azo compounds, diones and triones. While reactions involving radical anion intermediates were investigated as early as 1867 by *Berthelot*[1], it is only recently that they have been recognized as such.

This article surveys reported reactions in which a radical anion is an intermediate. Radical anion production has been reviewed extensively elsewhere[2,3]. Radical anion intermediates undergo the types of reactions shown in the following scheme:



Scheme 1.

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[**] The following abbreviations are used in this review: Et = ethyl, Bu = butyl, Ph = phenyl, Naph = naphthalene, DME = dimethoxyethane, THF = tetrahydrofuran, DMSO = dimethyl sulfoxide.

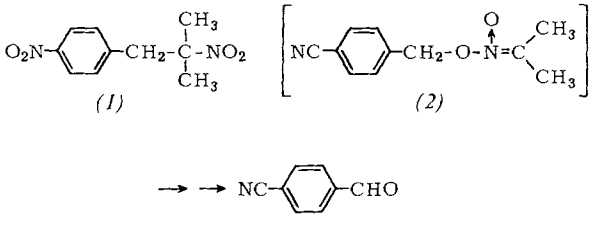
[1] *M. Berthelot*, Ann. Chim. *12*, 1955 (1867).

[2] *E. T. Kaiser* and *L. Kevan:* Radical Ions. Interscience, New York 1968, p. 783.

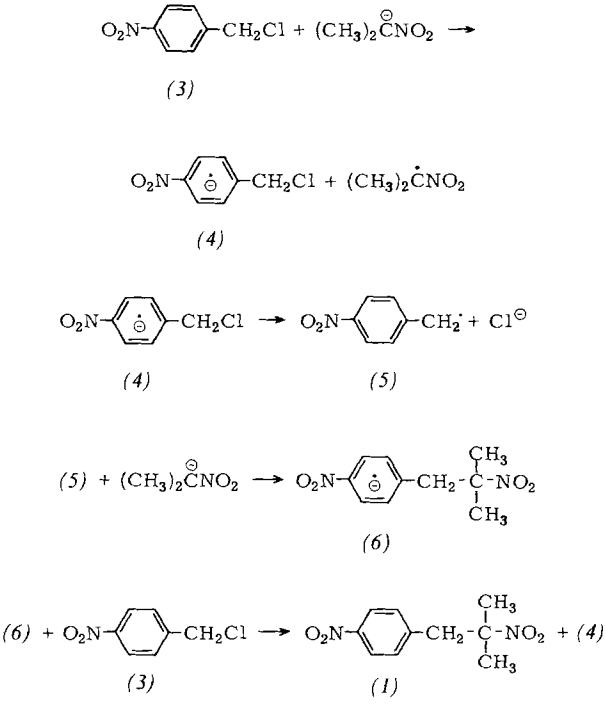
[3] *M. Szwarc*, Progr. Phys. Org. Chem. *6*, 323 (1968).

2. Radical Anions as Intermediates in Substitution Reactions

Most radical anion substitution reactions center upon the chemistry of nitroaliphatic and nitroaromatic compounds. For example, it has been known for some time that aromatic nitro groups promote unique reactions. In 1949 investigation of the reaction of various *para* substituted benzyl halides with the lithium salt of 2-nitropropane[4] revealed that *p*-nitrobenzyl chloride effects *C*-alkylation to give *(1)*. Benzyl halides substituted in the *para* position by CN, CF_3, $\oplus N(CH_3)_3$, CH_3CO, CH_3OCO, Br, or CH_3 undergo oxygen alkylation to *(2)*, which subsequently converts into the aldehyde.



Not only does *C*-alkylation depend upon the presence of a nitro group, but further, it occurs only if the nitro group is *ortho* or *para* to the benzyl position. Thus, when *p*-nitrobenzyl chloride is treated with 2-nitropropyllithium compound *(1)* is obtained in 83–95% yield[4–8]; *o*-nitrobenzyl chloride leads to formation of *C*-alkylation product in 46% yield[4]. On the other hand, *m*-nitrobenzyl chloride gives no *C*-alkylate, producing instead, *m*-nitrobenzaldehyde[4]. *p*-Nitrobenzyl bromide and iodide give *C*-alkylation products in 17 and 7% yield respectively[5,7].



Scheme 2.

[4] *H. B. Hass* and *M. L. Bender*, J. Amer. Chem. Soc. *71*, 1767, 3482 (1949).

[5] *N. Kornblum, P. Pink*, and *K. V. Yorka*, J. Amer. Chem. Soc. *83*, 2779 (1961).

The *C*-alkylation reactions of *o*-and *p*-nitrobenzyl chloride are now understood to be radical anion reactions[7,8]. *O*-alkylation, on the other hand, arises *via* a S_N2 pathway. The mechanism for the reaction of *p*-nitrobenzyl chloride with the 2-nitropropyl anion is shown in Scheme 2[9]. (For corresponding iodides and bromides the competing S_N2 process predominates and leads to *O*-alkylation.)

The nitro group in *(3)* serves to lower the reduction potential (Table 1) and promotes the formation of the radical anion *(4)*. Loss of chloride from *(4)* yields a resonance-stabilized free radical *(5)*. The chain nature of the mechanism is established by the observation that introduction of a small amount of a more easily reduced nitroaromatic compound, such as *p*-dinitrobenzene (Table 1), suppresses *C*-alkylation. Presumably this occurs as a result of removal of the electron from *(4)* by dinitrobenzene. The transfer of an electron between nitroaromatics is known to be often rapid[10].

Table 1. Polarographic data for substituted nitrobenzenes $R-C_6H_4-NO_2$ [11] in presence of 0.1 M tetra-*n*-propylammonium perchlorate in acetonitrile at 25 °C.

R	$-E_{1/2}$ (V)	R	$-E_{1/2}$ (V)	R	$-E_{1/2}$ (V)
p-NH_2	1.358	*p*-$CONH_2$	1.014	*m*-NH_2	1.208
p-OCH_3	1.250	*p*-SCN	0.96	*m*-CH_3	1.180
p-CH_3	1.203	*p*-$COOCH_3$	0.947	*m*-OCH_3	1.147
p-H	1.147	*p*-$COCH_3$	0.925	*m*-$COOCH_3$	1.044
p-F	1.128	*p*-CN	0.875	*m*-$COCH_3$	1.042
p-C_6H_5	1.103	*p*-CHO	0.863	*m*-CHO	1.016
p-Cl	1.063	*p*-SO_3CH_3	0.847	*m*-CN	0.938
p-Br	1.050	*p*-NO_2	0.69	*m*-NO_2	0.898
p-I	1.050	*p*-NO	0.525		

Reactions in which S_N2 substitution does not compete with the radical anion process have proven especially fruitful. Substitution reactions at the tertiary C-atom of cumyl chlorides preclude the S_N2 process since few, if any, authentic S_N2 displacements involving tertiary halides are known[12]. However, *p*-nitrocumyl chloride *(7a)* and α,*p*-dinitrocumene *(7b)* undergo facile substitution at the tertiary carbon with a variety of nucleophiles[13]. The reactions for *p*-nitrocumyl chloride and *p*-dinitrocumene are illustrated by the following scheme and the results listed in Table 2.

[6] *L. Weisler* and *R. W. Helmkamp*, J. Amer. Chem. Soc. *67*, 1167 (1945); *N. Kornblum* and *P. Pink*, Tetrahedron *19*, Suppl. 1, 17 (1963).

[7] *R. C. Kerber, G. W. Urry*, and *N. Kornblum*, J. Amer. Chem. Soc. *87*, 4520 (1965).

[8] *G. A. Russell* and *W. C. Danen*, J. Amer. Chem. Soc. *90*, 347 (1968); *N. Kornblum, R. E. Michel*, and *R. C. Kerber, ibid. 88*, 5606, 5662 (1966).

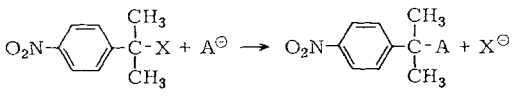
[9] Three other mechanisms for carbon alkylation were considered and rejected: a graded S_N1-S_N2 process, a carbene mechanism, and attack of 2-nitropropyl anion on the carbon of the ring bonding the CH_2Cl group. See *R. C. Kerber*, Ph. D. thesis, Purdue University 1965.

[10] See *e.g. S. I. Weissman*, Z. Elektrochem. *64*, 47 (1960); *R. L. Ward*, J. Chem. Phys. *32*, 410 (1960); *M. T. Jones* and *S. I. Weissman*, J. Amer. Chem. Soc. *84*, 4269 (1962).

[11] *A. H. Maki* and *D. Y. Geske*, J. Amer. Chem. Soc. *83*, 1852 (1961).

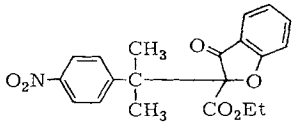
[12] *S. Winstein, S. Smith*, and *D. Darwish*, Tetrahedron Lett. *16*, 24 (1959).

[13] *N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser*, and *D. H. Snow*, J. Amer. Chem. Soc, *89*, 725 (1967); *89*, 5714 (1967); *N. Kornblum* and *F. W. Stuchal, ibid. 92*, 1804 (1970).



(7a), X = Cl
(7b), X = NO_2

(8)



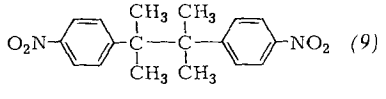
(8g)

Table 2. Tertiary substitution products in reactions of anions $A^{\ominus}$ [13, 14] with *p*-nitrocumyl chloride *(7a)* und α,*p*-dinitrocumene *(7b)*.

Product	A	(8), yield (%) with (7a)	(7b)
(8a)	$C(CH_3)_2NO_2$	65	71
(8b)	SPh	95	97
(8c)	$CH(COOEt)_2$	84	95
(8d)	C-*n*Bu$(COOEt)_2$	78	98
(8e)	1-Methyl-2-naphthyloxy	62	64
(8f)	NO_2	94	
(8g)	see above		70
(8h)	OPh		66
(8i)	CH_3NH_2	91	

Dependence of the substitution reaction on the presence of a *para* nitro group is again demonstrated by the failure of carbon substitution to occur in the comparable compounds lacking the *p*-nitro group[13]. For example, the analog of *(7a)* without a *p*-nitro group reacts to give α-methylstyrene, and whereas α-nitrocumene is not attacked by thiophenoxide, reaction with α, *p*-dinitrocumene *(7b)* to give compound *(8)* is complete in twenty minutes.

The radical anion substitution mechanism is consistent with these results. It is further substantiated by the importance of the *para* nitro group in forming a radical anion intermediate and accounts for other observations: light speeds the reaction by facilitating electron transfer from $A^{\ominus}$ to *(3)*; the dimer *(9)* is isolated in 1–5% yields; small amounts of *p*-dinitrobenzene or oxygen dramatically retard the substitution reaction[13].

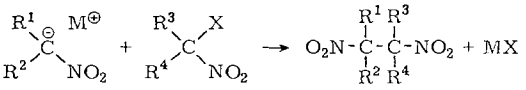


(9)

The importance of oxygen as a mechanistic probe in these reactions warrants further note. In the presence of oxygen yields from both *p*-nitrocumyl chloride *(7a)* and α,*p*-dinitrocumene *(7b)* are sharply reduced. For example, treatment of α,*p*-dinitrocumene with the anion of *n*-butylmalonic ester in the absence of oxygen leads to the *C*-alkylation product *(8d)* in 98% yield, while in the presence of oxygen this product is completely suppressed and *p*-nitrocumyl alcohol is formed in 80% yield[13]. These data support the intermediacy of a free radical[15].

A nitro group in the *meta* position offers an interesting study since it apparently cannot stabilize an intermediate benzylic free radical. Accordingly, there is no indication that *m*-nitrobenzyl chloride reacts by a radical anion pathway. However, *m*-nitrocumyl chloride and α, *m*-dinitrocumene result in high yields of tertiary substitution products which seem to arise *via* a radical anion process[16]. These reactions are slower than those with the nitro group in the *para* position. Since the *m*-nitrocumyl system, unlike *m*-nitrobenzyl chloride, cannot undergo S_N2 displacement, the radical anion substitution proceeds.

Some substitution reactions of nitroaliphatic compounds have also been investigated as possible radical anion reactions. Reactions of the 2-nitropropyl anion with 2-chloro- and 2-bromo-2-nitropropane, are known to be consistent with this mechanism[17]. *Russell* found that the reactions can be initiated photochemically or can be inhibited by hexaphenylethane or *p*-dinitrobenzene. The products in all cases are the *C*-alkyl derivates of the 2-nitropropyl anion. Earlier work has shown this dimerization to be a general one as long as R^1, R^2, R^3 and R^4, are alkyl and not hydrogen[18].



R^1-R^4 = Alkyl

3. Disproportionation

Aromatic hydrocarbons of sufficient electron affinity react with alkali metals to form mono-or divalent salts[19]. These salts are frequently observed to be in equilibrium, as shown in eq. 1.

$$2\ [R_2C{=}CR_2]^{\ominus}M^{\oplus} \rightleftharpoons [R_2\ddot{C}\text{-}\ddot{C}R_2]^{2\ominus}\ 2\ M^{\oplus} + R_2C{=}CR_2 \quad (1)$$

K is dependent upon structure, solvent, and cation. Furthermore, the radical anions in these equilibria are intermediates in dimerization and reduction reactions.

The effect of the cation and the solvent is interwoven, since the nature of the cation may exert controlling influences on the details of solvation[20–25]. As an example,

[14] *N. Kornblum, G. W. Earl, N. L. Holy, J. W. Manthey, M. T. Musser, D. H. Snow,* and *R. T. Swiger,* J. Amer. Chem. Soc. *89,* 6221 (1967).

[15] *G. A. Russell* and *W. C. Danen,* J. Amer. Chem. Soc. *88,* 5663 (1966); *G. A. Russell* and *A. G. Bemis, ibid. 88,* 5492 (1966).

[16] *N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, J. W. Manthey, M. T. Musser,* and *R. T. Swiger,* J. Amer. Chem. Soc. *90,* 6219 (1968).

[17] *G. A. Russell* and *W. C. Danen,* J. Amer. Chem. Soc. *90,* 347 (1968).

[18] *L. W. Seigle* and *H. B. Hass,* J. Org. Chem. *5,* 100 (1940).

[19] For leading references to works on alkali metal adducts of aromatic hydrocarbons see *A. Streitwieser Jr.:* Molecular Orbital Theory. Wiley, New York 1961, p. 159ff.

[20] A comprehensive discussion is given by *N. Kornblum, R. Selzer,* and *P. Haberfield,* J. Amer. Chem. Soc. *85,* 1148 (1963).

[21] *H. D. Zook* and *T. J. Russo,* J. Amer. Chem. Soc. *82,* 1258 (1960); *H. D. Zook* and *W. L. Gumby, ibid. 82,* 1386 (1960).

[22] H. E. Zaugg, B. W. Horrom, and *S. Borgwardt,* J. Amer. Chem. Soc. *82,* 2895 (1960); *H. E. Zaugg, ibid. 82,* 2093 (1960); *83,* 837 (1961).

[23] *J. F. Garst, D. Walmsley, C. Hewitt, W. R. Richards,* and *E. R. Zabolotny,* J. Amer. Chem. Soc. *86,* 412 (1964); *J. F. Garst, C. Hewitt, D. Walmsley,* and *W. R. Richards, ibid. 83,* 5034 (1961).

[24] *A. Streitwieser jr.* and *J. I. Brauman,* J. Amer. Chem. Soc. *85,* 2633 (1963).

[25] a) *J. F. Garst, J. G. Pacifici,* and *E. R. Zabolotny,* J. Amer. Chem. Soc. *88,* 3872 (1966); b) *J. F. Garst* and *R. S. Cole, ibid. 84,* 4352 (1962); c) *J. F. Garst* and *E. R. Zabolotny, ibid. 87,* 495 (1965); d) *E. Zabolotny* and *J. F. Garst, ibid. 86,* 1645 (1964).

K values for the equilibrium between tetraphenylethylene (T) and various alkali metals are shown in Table 3[25c]. The variations in K indicate that the equilibrium should include the effects of cation association or aggregation.

Table 3. Equilibrium constants (disproportionation constants) K for the equilibrium

$2[Ph_2C{=}CPh_2]^{\ominus}\ M^{\oplus} \rightleftarrows [Ph_2\ddot{C}\text{-}\ddot{C}Ph_2]^{2\ominus}2M^{\oplus} + Ph_2{=}CPh_2$ at 25 °C.

If K is dependent on concentration the upper and lower limits are given.

M	In diglyme	In DME	In THF
Li		0.3–1.3	0.7–1.2
Na		0.05–0.3	8–30
K	9–12	40–50	6000
Cs	200–400	2700	large

From Table 3 it is seen that K decreases as the solvent polarity increases from THF < DME < diglyme. The phenyl groups in the radical anion $T^{\dot{\ominus}}$ are not coplanar[3,26]; thus, the counterion cannot approach close to the negative charge. On the other hand, coplanarity of the phenyl groups in the dianion is permitted through rotation about the central C-C axis to form a skewed conformation which allows for close approach of the counterions to the CPh_2 centers. Whereas the $T^{2\ominus}$, $2M^{\oplus}$ forms contact ion pairs, the $T^{\dot{\ominus}}M^{\oplus}$ forms solvent-separated pairs. The salt of the radical anion is therefore more sensitive to solvation effects than the salt of the dianion[27,28] and is favored by increasing solvent polarity.

The disproportionation shown in eq. 1 is dependent upon the structure of the radical anion. Radical anion disproportionation increases with increasing steric strain in arylethylenes. Table 4 shows that tetraphenylethylene and stilbene differ in K values by more than 10^4. By one interpretation[25a] disproportionation is accompanied by relief of steric strain because dianions are presumed to form skewed conformations while the ethylene structure of the radical anions are constrained to planarity. According to an alternative interpretation[27] the electron-electron repulsions in the stilbene dianion are greater

Table 4. Equilibrium constants (disproportionation constants) K [a] of arylethylenesodium compounds in 2-methyltetrahydrofuran at 25 ° C [25].

Hydrocarbon	K
α-Methylstilbene	1000
Stilbene	0.09
Triphenylethylene	36
Tetraphenylethylene	1000

[a] K is the equilibrium constant for disproportionation of ion pairs according to eq. 1. The concentration of ionic species ranged from *ca.* 10^{-5} to *ca.* 10^{-3} mole/l; K is concentration independent through this range.

than those of tri- or tetraphenylethylene (the phenyl groups promoting charge dispersal), so the radical anion side of the equilibrium is favored in the stilbene system.

The former argument seems preferable since methyl substitution of stilbene results in at least a 10^4 fold increase in K. It is anticipated that the effect of methyl substitution on electron-electron repulsion would be greater in the dianion than in the radical anion, but this implies a decrease in the value of K, the opposite of what is observed. Thus, the result of methyl substitution is best viewed as a steric effect reflecting a change in geometry accompanying disproportionation.

The effect of the cation upon K is dependent upon the ethylene structure. Disproportion of radical anions derived from stilbene increases as the size of the cation decreases. This trend is the reverse of that observed in tetraphenylethylene systems. It is likely that the radical anion of stilbene, as well as its dianion, forms a contact pair[3]. Ion pairing favors disproportionation because the binding of two counterions by a dianion is more than twice as powerful as the attraction of the radical anion and its partner. Thus, the stronger binding of a small counterion would lead to greater disproportionation. In the tetraphenyethylene system the radical anion forms a solvent-separated pair, whereas the dianion remains a contact pair. Solvation of the cation contributes to the stability of the radical anion and becomes increasingly important with small cations.

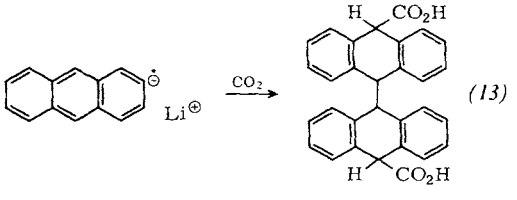
Coupling and/or reduction are possible reactions of the radical anion. When tolan is treated with an excess of sodium naphthalenide in THF[29], an initial rapid electron transfer occurs with formation of the radical anion *(10)*, followed by formation of either the dimer *(11)* or the monomer dianion *(12)*.

$$Ph\text{-}C{\equiv}C\text{-}Ph \xrightarrow{Naph^{\dot{\ominus}}} Ph\text{-}C{\equiv}C\text{-}Ph^{\dot{\ominus}} \qquad (10)$$

$$2\ Ph\text{-}C{\equiv}C\text{-}Ph^{\dot{\ominus}} \longrightarrow Ph\text{-}\ddot{C}{=}\underset{\underset{Ph}{|}}{C}\text{-}\underset{\underset{Ph}{|}}{C}{=}\ddot{C}\text{-}Ph \qquad (11)$$

$$Ph\text{-}C{\equiv}C\text{-}Ph^{\dot{\ominus}} \xrightarrow{Naph^{\dot{\ominus}}} Ph\text{-}\ddot{C}{=}\ddot{C}\text{-}Ph \qquad (12)$$

When an excess of tolan is present *(12)* does not form though *(11)* does. Formation of *(11)* is analogous to the coupling of anthracene radical anion *(13)* reported earlier[30]. Other examples are reviewed by *Birch*[31].



(13)

[26] G. Favini and *M. Simonetta*, Theoret. Chim. Acta *1*, 294 (1963).

[27] *N. S. Hush* and *J. Blackledge*, J. Chem. Phys. *23*, 514 (1955).

[28] For additional references to the effect of solvent on the tetraphenylethylene equilibrium see: *W. Schlenk, J. Appenrot, A. Michael*, and *A. Thal*, Ber dtsch. chem. Ges. *47*, 473 (1914); *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 1 (1928); *N. B. Keevil* and *H. E. Bent*, J. Amer. Chem. Soc. *60*, 193 (1938); *H. Gilman* and *R. V. Young*, J. Org. Chem. *1*, 315 (1936).

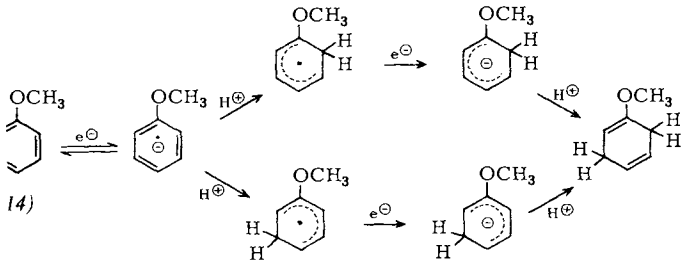
[29] *D. A. Dadley* and *A. G. Evans*, J. Chem. Soc. *B 1968*, 107.

[30] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 83 (1928).

[31] *A. J. Birch*, Quart. Rev. Chem. Soc. *4*, 69 (1950).

[32] For mechanistic studies see, *e.g.*: *A. P. Krapbo* and *A. A. Bothner-By*, J. Amer. Chem. Soc. *81*, 3658 (1959); *A. J. Birch* and *D. Nasipun*, Tetrahedron *6*, 148 (1958); *W. Huchel, B. Graf*, and *D. Munker*, Liebigs Ann. Chem. *614*, 47 (1958); *J. F. Eastham* and *D. R. Larkin*, J. Amer. Chem. Soc. *81*, 3652 (1959).

In the Birch reduction the intermediacy of a radical anion is well supported[32]. The mechanism for the reduction of anisole *(14)* is just one example[33].

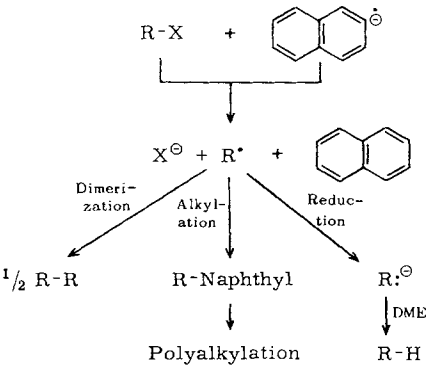


14)

4. Radical Anions of Aromatic Hydrocarbons

It has been known for more than 100 years that aromatic hydrocarbons may react with alkali metals. The first real description (though not expressed in modern terms) is attributed to *Schlenk*[34]. More recently the formation and reactions of these adducts have been interpreted in terms of radical anion intermediates.

On treating naphthalene with metallic sodium a salt is formed that exhibits a variety of reactions: substitution, equilibrium, and oxidation-reduction. Often these processes occur simultaneously. For example, treatment of sodium naphthalenide with alkyl halides in 1,2-dimethoxyethane (DME) leads to oxidation-reduction[35,36], alkylation[37,38], and dimerization products[35] (see Schemes 3 and 5).



Scheme 3.

Table 5. Yield of aliphatic hydrocarbons in the reaction of sodium naphthalenide with RCH_2CH_2X [35].

X	R	Yield (%) of $R(CH_2)_4R$	RCH_2CH_3	$RCH=CH_2$
Cl	$CH_3(CH_2)_2$	0	44	0
Br	$CH_3(CH_2)_2$	5.0	29	0
I	$CH_3(CH_2)_2$	56	17	3.7
I	$CH_3(CH_2)_4$	50	22	6

Obviously no more than part of the reduction products can be accounted for by a disproportionation of the radical *(15)*. Two mechanisms [*via* the anion *(16)* and the radical *(17)*] have been suggested[35].

$$2\ RCH_2CH_2^{\bullet} \longrightarrow RCH{=}CH + RCH_2CH_3$$
(15)

$$RCH_2CH_2^{\bullet} + Naph^{\ominus} \longrightarrow RCH_2CH_2{:}^{\ominus} + Naph$$
(15) *(16)*

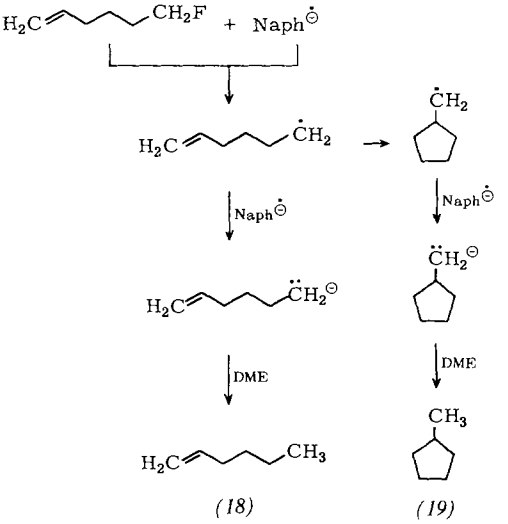
$$RCH_2CH_2{:}^{\ominus} \xrightarrow{DME} RCH_2CH_3 + CH_3OCH{=}CH_2 + {}^{\ominus}OCH_3$$

$$RCH_2CH_2^{\bullet} \xrightarrow{DME} RCH_2CH_3 + CH_3OCH_2\dot{C}HOCH_3$$
(15) *(17)*

$$CH_3OCH_2\dot{C}HOCH_3 \xrightarrow{Naph^{\ominus}} CH_3OCH_2\ddot{C}HOCH_3 \longrightarrow CH_3OCH{=}CH_2 + {}^{\ominus}OCH_3$$

Alkyl halide reduction products (R-H) arise through disproportionation or successive electron-transfer reactions. Reaction of sodium naphthalenide with *n*-propyl and *n*-pentyl halides[35], like other halides[36], results in a rather large difference in yield between the reduction and oxidation products. (Table 5).

Studies on 5-hexenyl fluoride are helpful in choosing between *(16)* and *(17)*. *Garst* found that the reduction of



Scheme 4.

[33] *I. K. Brown, D. R. Burnham,* and *N. A. Rogers,* Tetrahedron Lett. *1966,* 2621.

[34] First reported by *W. Schlenk, J. Appenrodt, A. Michael,* and *A. Thal,* Ber. dtsch, chem. Ges. *47,* 473 (1914); later important papers in this area are: *R. Willstätter, F. Seitz,* and *E. Bumm, ibid. 61,* 871 (1928); *W. Schlenk* and *E. Bergmann,* Liebigs Ann. Chem. *463,* 1 (1928); *464,* 1 (1928).

[35] *G. D. Sargent, J. N. Cron,* and *S. Bank,* J. Amer. Chem. Soc. *88,* 5363 (1966).

[36] a) *J. F. Garst, P. W. Ayers,* and *R. C. Lamb,* J. Amer. Chem. Soc. *88,* 4260 (1966); b) Preprints, Meeting Amer. Chem. Soc., Div. Petrol. Chem. *13,* D65 (1968); c) *J. F. Garst* and *F. E. Barton,* Tetrahedron Lett. *1969,* 587.

[37] *D. Lipkin, F. R. Galiano,* and *R. W. Jordan,* Chem. Ind. (London) *1963,* 1957; *D. Lipkin, G. J. Divis,* and *R. W. Jordan,* Preprints, Meeting Amer. Chem. Soc., Div. Petrol. Chem. *13,* D61 (1968).

[38] *N. D. Scott* and *J. F. Walker,* US-Pat. 2 150 039 (1939).

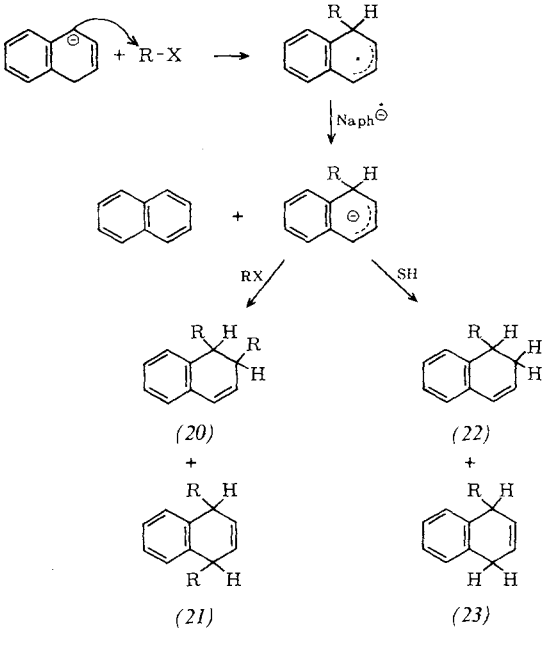
5-hexenyl fluoride with sodium naphthalenide yielded 1-hexene *(18)* and methylcyclopentane *(19)*; the reaction path given in Scheme 4 has been suggested[36b].

With an excess of sodium naphthalenide the ratio 1-hexene:methylcyclopentane is as much as 40:1; it never falls below 2:1. Consequently, the reaction path *via (17)* is less likely than that *via (16)* because it is known that cyclization of these radicals is much faster than hydrogen atom transfer[36a,39].

Dimerization of the alkyl moiety conceivably could occur either by the coupling of free radicals or through displacement. To determine the origin of the dimer a mixture of *n*-propyl and isopropyl iodides was treated with sodium naphthalenide. The hexanes produced were isolated in statistical yields[35], a result consistent with a coupling process, but not with displacement[40–43].

Another interesting facet of the dimerization process is the observation that dimer formation is significant only for alkyl iodides. Apparently, because the reactions of alkyl iodides are very fast, the concentration of radical is sufficient to render dimerization competitive with other processes. With fluorides, chlorides, and bromides little dimer is formed and there is an increase in reduction products (Table 5).

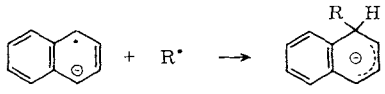
Diverse mechanisms are suggested to account for the formation of alkylation products. *Lipkin* proposes an initial S_N2 attack on the alkyl halide by a nucleophilic radical anion[37] (Scheme 5).



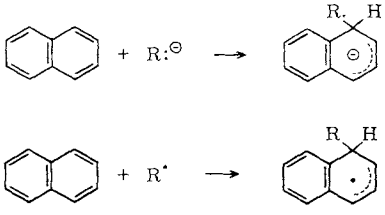
Scheme 5. SH = solvent

Subsequent reduction of the resulting free radical leads to a carbanion, which can attack another molecule of alkyl halide to form the products *(20)* and *(21)* and/or abstract a proton from the solvent to form *(22)* and *(23)*.

Another mechanism proposes "free radical" type combination of an alkyl free radical with the aromatic radical anion as the initiation step by which alkylation takes place[44].



Two additional variations postulate attack by an alkyl radical or alkyl anion on naphthalene[44,45]. Both reactions lead to intermediates common to the other mechanisms.



Preliminary evidence is more in accord with the combination of two radicals as the mechanism by which the formation of alkylation product is initiated. Support for this view comes from three observations: 1) The yield of alkylation is independent of halide[46]. 2) From Table 6 it is seen that the yield of alkylation product follows the order, tertiary > secondary > primary[44]. Both of these observations would discount a displacement (S_N2) mechanism. The observation that the alkylation product is wholly insensitive to the presence of excess naphthalene[44] suggests that mechanisms in which naphthalene couples with either an alkyl radical or a carbanion are not product controlling.

Table 6. Product distribution from the reaction of sodium naphthalenide with alkyl iodides RI [44].

Products	Relative yield (%) from			
	$(CH_3)_3CCH_2I$	*n*-$C_5H_{11}I$	*sec*-$C_5H_{11}I$	*tert*-$C_5H_{11}I$
Total aliphatic	89	65	52	39
including R-R	72	46	22	3
R-H	17	16	17	22
Alkene		3	4	8
			9	6
Total alkylation products	11	35	48	61
Aliphatic/ alkylation products	8.1	1.9	1.1	0.64
Dialkylation/ monoalkylation products	0	2.5	0.72	0

[39] *R. C. Lamb, P. W. Ayers,* and *M. K. Toney,* J. Amer. Chem. Soc. *85,* 3483 (1963).

[40] *J. A. Kerr* and *A. F. Trotman-Dickenson,* Progr. Reaction Kinetics *1,* 105 (1961); *A. F. Trotman-Dickenson,* Annu. Rep. Chem. Soc. *55,* 41 (1958).

[41] The tacit but necessary assumption that both radicals are produced at the same rate is supported by data which suggest that the rate of reaction of both halides with sodium naphthalenide should be diffusion controlled; *D. J. Morantz* and *E. Warhurst,* Trans. Faraday Soc. *51,* 1375 (1955).

[42] Nucleophilic displacement reactions on *n*-propyl exceed rates on isopropyl by at least a factor of ten; *A. Streitwieser, Jr.*: Solvolytic Displacement Reactions. McGraw-Hill, New York 1962, pp. 11–13; Chem. Rev. *56,* 571 (1956).

[43] For nucleophiles of hard basicity the competing E2 elimination is more significant for isopropyl than propyl halides: See, for example, *M. L. Dahr, E. D. Hughes, C. K. Ingold,* and *S. Masterman,* J. Chem. Soc. *1948* 2055.

[44] *G. D. Sargent* and *G. A. Lux,* J. Amer. Chem. Soc. *90,* 7160 (1968).

[45] *G. J. Hoijtink,* Chemie-Ing.-Techn. *35,* 333 (1963).

[46] *J. F. Garst, J. T. Barbas,* and *F. E. Barton II,* J. Amer. Chem. Soc. *90,* 7159 (1968).

This observation is interesting, particularly in view of data to follow concerning reactions of alkyllithium with anthracene. In a system that is analogous to the reaction of sodium naphthalenide with alkyl halides, anthracene undergoes a photolytically catalyzed alkylation reaction with various alkyllithium reagents[47] (see Table 7).

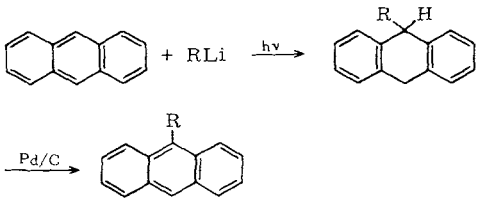


Table 7. Reaction of alkyllithium RLi with anthracene [a].

Solvent	R	Yield (%) of R-Anthracene	Yield (%) of 9,10-Dihydroanthracene
Ethyl ether	CH_3	0	0
THF	CH_3	0	37
THF	C_2H_5	74	0
THF	n-C_4H_9	66	0

[a] The fate of all alkyl moiety is not clear. Dimer formation is not reported.

Evidence does not point to attack by alkyllithium on the anthracene radical anion. With *n*-butyllithium no ESR evidence is found for a 9-butylanthracene radical anion. (The anthracene radical anion is present.) Also, if lithium anthracenide is prepared independently and treated with *n*-butyllithium there is less alkylation and more 9,10-dihydroanthracene formation. The dihydroanthracene possibly derives from dianion, which would be more probable here than under normal alkylation conditions. Photolyses performed on other hydrocarbons in the presence of *n*-butyllithium show that the reactivity of the hydrocarbon decreases in the order anthracene, phenanthrene, naphthalene, biphenyl[47]. This may be a consequence of differences in absorption of the UV light used to catalyze the reaction, or of the variations in electron affinity of these hydrocarbons[48].

It is tempting to view the process as one involving the transitory existence of a radical anion formed by electron transfer from alkyllithium to anthracene in a solvent cage, followed by collapse of the two species. Such a process would be consistent with the best supported mechanistic proposal for the reaction of sodium naphthalenide with alkyl halides. This route, however, seems unlikely in view of the results of other photonucleophilic aromatic substitution reactions. Such reactions include hydroxylation[49,50], amination[50,51], cyanation[52], halogenation[53], and alkoxylation[54]. These reactions apparently proceed by aromatic excitation to the S_1 state followed by coupling with the nucleophile rather than an electron transfer process[55].

Another process shown to have a radical anion pathway is the reaction of sodium naphthalenide with alkyl toluenesulfonates[56], which leads to alcohols in good yield (see Table 8).

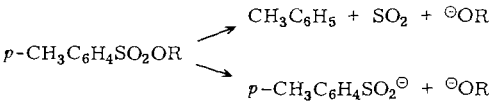


Table 8. Cleavage of toluenesulfonates p-$CH_3C_6H_4SO_2R$ with sodium naphthalenide to alcohols ROH [57].

R	Yield of ROH (%)
Cyclohexyl	100
Cyclopentyl	98
cis-4-Cyclooctenyl	98
Menthyl	98
trans-2-Phenylcyclohexyl	93
Cholesteryl	95
Phenyl	99
Stearyl	99
Neopentyl	85

Other arene radical anions may be used. Phenanthrene-sodium appears to be quite suitable, whereas anthracene-sodium reacts much more slowly and gives poorer yields (*ca.* 50% with cyclohexyl toluenesulfonate). Sodium diphenylketyl does not reduce sulfonates even though the reduction potential of benzophenone ($-E_{1/2}$ = 1.22 V)[58] is comparable to that of anthracene ($-E_{1/2}$ = 1.46 V)[59]. Reduction of toluenesulfonates by sodium in ammonia[60] and sodium amalgam in ethanol[61] also produces alcohol, conceivably *via* a radical anion route.

Phenyl radical anions show a rather small neighboring group effect. It is conceivable that a phenyl radical anion could participate either directly or as an electron transfer agent (Scheme 6, above and below)[62].

Cram found[62] that upon treatment of *threo*-2-phenyl-3-pentyl methanesulfonate with potassium in DME 94% of the product was 2-phenylpentane and 6% was 3-

[47] *H. J. S. Winkler, R. Bollinger,* and *H. Winkler,* J. Org. Chem. *32,* 1700 (1967).

[48] *H. J. S. Winkler* and *H. Winkler,* J. Org. Chem. *32,* 1965 (1967).

[49] *E. Havinga, R. O. de Jongh,* and *W. Dorst,* Recl. Trav. Chim. Pays-Bas. *75,* 378 (1956).

[50] *E. Havinga,* Pure Appl. Chem. *16,* 137 (1968); *E. Havinga* and *R. O. de Jongh,* Bull. Soc. Chim. belges *71,* 803 (1962); *R. O. de Jongh* and *E. Havinga,* Recl. Trav. Chim. Pays-Bas *87,* 1318 (1968); *S. de Vries* and *E. Havinga, ibid. 84,* 601 (1965).

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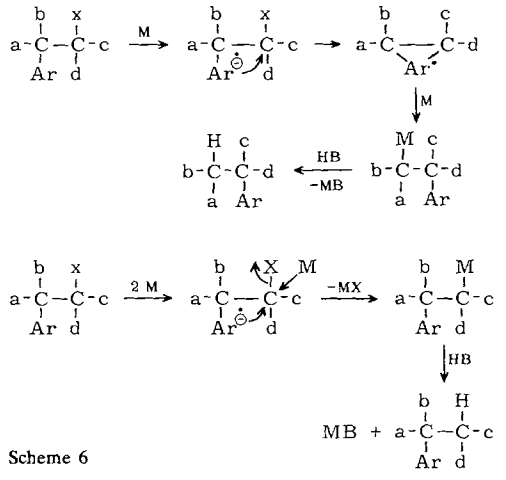
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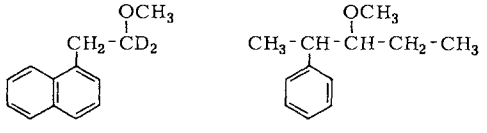
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Scheme 6

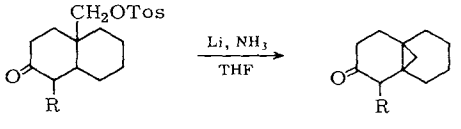
phenylpentane (the product of phenyl migration). Treatment of *threo*-3-phenyl-2-pentylmethane sulfonate with sodium in liquid ammonia gave 75% 3-phenylpentane and 3% 2-phenylpentane (the product of phenyl migration). Conceivably rearrangement could also result from phenyl migration to a carbon radical or organometallic compound. But aryl radical anion participation seems more appropriate in view of the fact that 1,2-phenyl migration to carbon radicals[63] or to carbon bonded to metal[64] occur only in systems widely different than the above.

A result which seems to confirm electron transfer as a neighboring group effect is the reduction of 1,1-dideuterio-1-methoxy-2-(1-naphthyl)ethane *(24)* with potassium. Reduction occurs *readily* and without rearrangement. Reduction of *threo*-2-phenyl-3-methoxypentane *(25)*, by comparison, is extremely slow. These experiments demonstrate the necessary role of the naphthyl group in the reduction process and imply neighboring group participation by electron transfer.



(24) *(25)*

There is one other example of a reaction in which a radical anion might have served as a neighboring group; this involves the conversion of *(26)* to *(27)*[65].



(26) *(27)*

[63] For a summary see *D. J. Cram* in *M. S. Newman:* Steric Effects in Organic Chemistry. McGraw-Hill, New York 1956, p. 283.

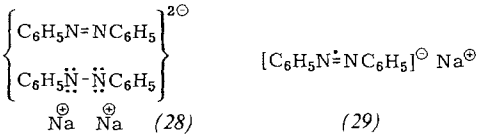
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5. Azo Radical Anions

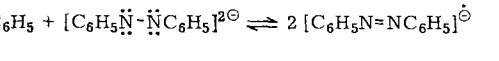
The existence of a 1:1 adduct of sodium with azobenzene was recognized by *Schlenk*[66]. However, he formulated the product *(28)* rather than the radical anion *(29)*.



(28) *(29)*

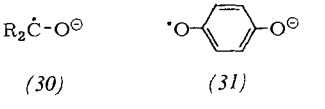
The intermediacy of radical anions can be inferred from work showing that the "di-Grignard" reagent of hydrazobenzene readily reduces benzoin and that azobenzene oxidizes many organometallic compounds[67]. For example, azobenzene is reduced to a salt of hydrazobenzene when treated with phenyllithium or phenyl magnesium bromide, both of which undergo coupling to biphenyl[68]. *Gilman* and *Adams*[69] showed that the formation of biphenyl did not involve triphenylhydrazine anion as an intermediate.

Wittig[70] described a crystalline salt of a radical anion prepared by the reaction of azobenzene with the lithium salt of azobenzene, though it is now known that the equilibrium lies far to the left.



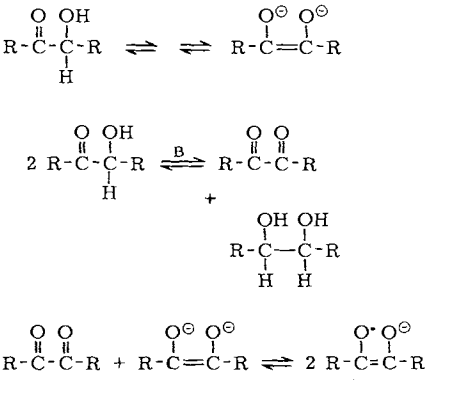
6. Diones and Triones

The chemistry of ketyl *(30)* and semiquinone *(31)* radical anions is well known. Ketyls are intermediates in the pinacol reaction; semiquinones are particularly important as electron carriers in certain biological systems. Less well known are the reactions of semidiones and semitriones.

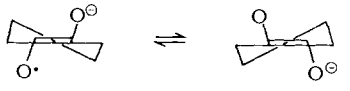


(30) *(31)*

Radical anions of diones are produced by electrolytic reduction or reaction of the appropriate α-hydroxy ketones in DMSO containing an excess of potassium *tert*-butoxide[71]. These radical anions have been shown to have considerable stability even when R is alkyl or hydrogen.

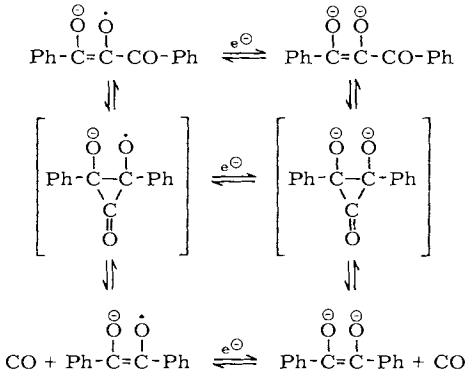


The study of semidiones has largely centered in the area of conformational analysis. For example, *Russell* has examined the semidiones of various cycloalkanes[72]. The effect of temperature on the population in the equatorial (more stable) and axial conformations of the methylcyclohexanesemidiones yields enthalpy differences of 0.7 and 1.4 ($\Delta S = 0$) for the 3- and 4-methyl substituents. Cyclohexanesemidione *(32)* undergoes the interconversion of half-chair conformations with an enthalpy of activation of 4.0 kcal/mole, entropy of activation +1 eu.



(32)

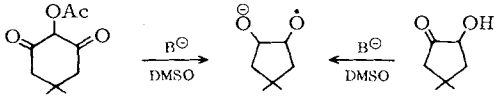
Semitriones are produced by polarographic and electrolytic reductions. Reduction of a triketone often leads to a rearrangement. For example, 1,3-diphenyl-1,2,3-propanetrione loses carbon monoxide and is converted to the semidione (in equilibrium with the dianion) most likely according to the reactions given in Scheme 7[73].



Scheme 7

This route is supported by the fact that ^{14}C-labeling at C-1 and C-3 yields carbon monoxide devoid of radioactivity[74].

Ring contraction is known to occur in at least one case[73]. Reaction of 2-acetoxy-5,5-dimethylcyclohexane-1,3-dione or 4,4-dimethyl-2-hydroxycyclopentanone with potassium *tert*-butoxide in DMSO yields a five-line sextet consistent with four equivalent hydrogen atoms, a_H = 12.8 gauss.



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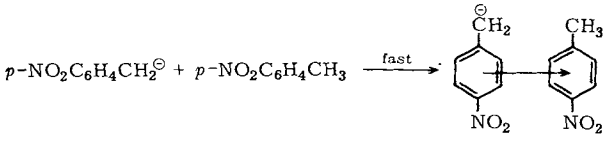
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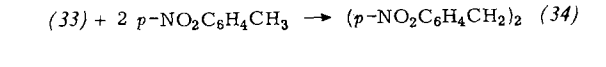
7. Other Reactions of Nitro Compounds

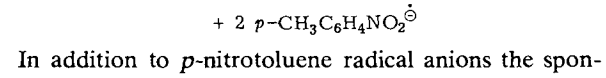
In section 2 it was noted that nitroaromatic systems are good electron acceptors. Reactions other than substitution are known to proceed through a reactive radical anion intermediate. For example, treatment of *o*- and *p*-nitrotoluene with base, and the resultant disproportionation products have been studied by a number of earlier workers[75].

A more recent investigation with potassium *tert*-butoxide in *tert*-butyl alcohol or with dimethyl sulfoxide (DMSO), has shown formation of the *p*-nitrotoluene radical anion in the absence of oxygen[76,77]. This process is spontaneous and derives from reduction of the parent nitrotoluene by ionization products of the nitrotoluene.



(33)





In addition to *p*-nitrotoluene radical anions the spontaneous disproportionation (in the absence of oxygen) of *p*-nitrotoluene in basic *tert*-butyl alcohol produces *p,p'*-dinitrobibenzyl *(34)* and insoluble products (Table 9)[77].

Table 9. Spontaneous dimerization of *p*-nitrotoluene in *tert*-butanol/potassium *tert*-butoxide at 25 °C.

Reaction time (min)	Yield of *(34)* (%)	Recovered *p*-nitrotoluene	Benzene-insoluble materials (%)
5	21	69	0
10	37	56	0.4
20	41	51	1.5
30	47	a	+
60	57	a	++

[a] Not measured.

p-Nitrotoluene in a mixture of 80% DMSO and 20% *tert*-butyl alcohol, however, yields additional products, namely *p,p'*-dinitrostilbene and its radical anion. Stilbene derives from the bibenzyl product and is apparently connected with the fact that *p,p'*-dinitrobibenzyl is soluble in DMSO but not in *tert*-butyl alcohol.

[75] *W. K. Perkin,* J. Chem. Soc. *37,* 546 (1880); *H. Klinger,* Ber. dtsch chem. Ges. *16,* 941 (1883); *F. Bender* and *G. Schultz, ibid. 19,* 3234 (1886); *O. Fischer* and *E. Hepp, ibid. 26,* 2231 (1893); *A. G. Green,* J. Chem. Soc. *85,* 1424 (1904); *A. G. Green, F. Marsden,* and *F. Scholefield, ibid. 85,* 1432 (1904); *A. E. Green, A. H. Davis,* and *R. S. Horsfall, ibid. 91,* 2076 (1907); *A. J. Plisov,* Ukr. Khim. Zh. *4,* 241 (1929); *A. E. Porai-Koshitz,* Anilinokrasochnava Prom. *4,* 261 (1934); Chem. Abstr. *23,* 139 (1935); *H. O. House,* Org. Synth. Coll. Vol. *4,* 367 (1963); *F. W. Bergstrom, I. M. Granara,* and *V. Erickson,* J. Org. Chem. *7,* 98 (1942); *W. Bradley* and *R. Robinson,* J. Chem. Soc. *135,* 1254 (1932); *H. Klinger* and *R. Pitschke,* Ber. dtsch. chem. Ges. *18,* 2551 (1885); *R. Scholl,* Monatsh. Chem. *34,* 1011 (1913).

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In the presence of oxygen, treatment of *p*-nitrotoluene with potassium *tert*-butoxide in *tert*-butyl alcohol yields *p,p*'-dinitrobibenzyl plus *p*-nitrobenzoic acid *(35)*[78]. Molecular oxygen can replace the un-ionized *p*-nitrotoluene as an electron acceptor. It also converts the *p*-nitrotoluene radical anion into *p*-nitrotoluene, so that higher ultimate yields of dimer can be achieved in the presence of oxygen than in its absence. The *p*-nitrobenzoic acid is formed in a competing process whose rate is dependent upon oxygen pressure.

$$p\text{-}NO_2C_6H_4\overset{\ominus}{C}H_2 + O_2 \longrightarrow p\text{-}NO_2C_6H_4CH_2OO^{\ominus}$$
$$\downarrow$$
$$p\text{-}NO_2C_6H_4CO_2^{\ominus} \quad (35)$$

Mechanisms involving the coupling of *p*-nitrobenzyl radicals in the presence of molecular oxygen can be excluded by the known rapidity of the reactions of molecular oxygen with alkyl radicals, including those of the *p*-nitrobenzyl type.

A similar type of behavior is shown in the reactions of aliphatic polynitro compounds. Formation of unstable radical anions of tri- and tetranitromethane by electron transfer from a number of carbanions is followed by loss of a nitro group in each case[79]. $[(NO_2)_2CH]^{\cdot 2\ominus}$ is eventually detected from trinitromethane and $[(NO_2)_3C]^{\cdot 2\ominus}$ is the decomposition product of tetranitromethane. Treatment of the related nitroalkane, 1,1,1-trinitroethane, with butyl thiolate and 2-nitropropyl anions leads to the dimers of the anion in yields of 71 and 87% respectively[80].

Organic reaction pathways involving radical anions are numerous and varied. This review has not exhausted the extant applications; additional examples are likely, as are further investigations into the aspects cited here.

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COMMUNICATIONS

Myrmicacin, The First Insect Herbicide[**]

By *Hermann Schildknecht* and *Knut Koob*[*]

The leaf-cutting ants, *e.g. Atta sexdens* from South America, demonstrate a uniquely effective way of establishing and maintaining their "fungus gardens" as a source of food. Until now the mechanism by which this is accomplished – under growth conditions favorable to many microorganisms – has not been resolved. Equally mysterious was the method by which harvest ants succeeded in preserving gathered grain in storerooms for long periods of time without sprouting.

From the metathoracic glands of Myrmicine ants we have isolated and identified β-indolylacetic acid (IAA)[1] and phenylacetic acid (PAA)[2]. *Martin*'s[3] investigation of leaf-cutting ants revealed – contrary to *Weber*'s suggestion[4] – neither the presence of growth regulators nor of antibiotics.

Thin-layer chromatography of the secretion of the metathoracic glands followed by treatment with concentrated sulfuric acid revealed a previously unidentified substance, which we called Myrmicacin, between the PAA- and IAA-spots. Again, all the usual reactions indicated a carboxylic acid. We succeeded with its micro-preparative isolation gas-chromatographically after silylation of the thin-layer band. From the molecular weight of the silylated Myrmicacin (332.229271), obtained by mass spectrometry, we deduced the formula $C_{10}H_{20}O_3$. For structural analysis, using a combination of mass spectrometry and gas chromatography, we prepared the methyl ester with diazomethane. We found the fragment mass 103 to be a key fragment, which indicated a β-hydroxy ester. After subtraction of this key fragment there remained a C-7 fragment, which was easily detected in the mass spectrum of the silylated carboxylic acid. Thus, as the result of mass spectral analysis we found the β-hydroxydecanoic acid *(1)* and also – as further analysis of the secretion showed – β-hydroxyoctanoic *(2)* and β-hydroxyhexanoic acid *(3)*; see Table 1. Myrmicacin *(1)* was found to be the levorotatory D-acid with $[\alpha]_D^{20} = -3°$ (in $CHCl_3$).

Table 1. Concentrations of the acids in the metathoracic glands of the leaf-cutting ants *(A. sexdens)*.

Acids		Conc. (μg/gland)
Phenylacetic acid	PAA	1.3 - 3.0
Indolylacetic acid	IAA	0.01 - 0.1
D-β-Hydroxydecanoic acid (Myrmicacin)	*(1)*	2.0 - 3.5
β-Hydroxyoctanoic acid	*(2)*	0.5 - 5.0
β-Hydroxyhexanoic acid	*(3)*	<0.1

$CH_3\text{-}(CH_2)_6\text{-}CHOH\text{-}CH_2\text{-}COOH$
(1)

$CH_3\text{-}(CH_2)_4\text{-}CHOH\text{-}CH_2\text{-}COOH$
(2)

$CH_3\text{-}(CH_2)_2\text{-}CHOH\text{-}CH_2\text{-}COOH$
(3)

The carboxylic acids in Table 1 were also detected in other ants by gas-chromatographic techniques; see Table 2.

Table 2. Acids from the metathoracic glands of ants.

Kind of ant	Myrmicacin	PAA	IAA	*(2)*	*(3)*
Atta sexdens	+	+	+	+	+
Messor barbarus L.	+	+	–	–	–
Myrmica laevinodis Nyl.	+	+	+	–	–
Acromyrmex sp.	+	–	+	–	–

The occurrence of hydroxy acids together with the bioregulators IAA and PAA suggested that they too may be growth regu-

lators. Since the seed-storing ant *Messor* does not have the growth regulator IAA but does produce Myrmicacin, the hydroxy acids could be expected to have a germination-inhibiting effect. In support of this hypothesis the fungicide test[5] showed that Myrmicacin in a concentration of 0.015% has an effectiveness of 25% for growth inhibition of *Altenaria tennis* and *Botrytis cinerea*, and in a concentration of 0.03%, it is 90% effective. The fungicidal activity of Myrmicacin can be demonstrated very vividly by adding 20 mg of the latter to 100 g of plum puree. For three weeks the puree was not attacked by fungi or fruit flies, while in the same time the control puree lacking Myrmicacin was completely overgrown with microorganisms.

Thus we conclude that the harvest ants prevent the gathered grass seeds from sprouting and the leaf-cutting ants prevent the intruding spores from sprouting by using Myrmicacin as a herbicide. Additional preliminary experiments show that PAA inhibits bacterial growth in the garden, and IAA supports the growth of the mycelia[6]. Thus only the symbiotic fungus is able to thrive at the founding of a new nest because it is brought as mycelia by queen ants after their nuptial flight[7]. All the other fungi which intrude as spores remain undeveloped. Whether or not the bulbous thickenings which are formed under the care and control of the ants at the ends of the mycelia and which are used as food for the ants and whether their young develop with the help of the compounds secreted by the metathoracic glands is still being investigated.

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[**] Defensive compounds in arthropods Part 50. – Part 49: *H. Schildknecht* and *D. Hotz*, Proc. Third Steroid Congress, Excerpta Medica, in press.

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Complexes of Phosphirane

By *R. Bausch, E. A. V. Ebsworth*, and *D. W. H. Rankin*[*]

Attempts to add or remove a proton from the phosphorus atom in the small ring compound phosphirane, $(CH_2)_2PH$, have not been successful. Reaction with protonic acids is rapid, and leads to liberation of ethylene[1]; with potassium in liquid ammonia there is a complicated reaction to give the anions of different phosphanes without liberation of hydrogen. Similarly, reaction of phosphirane with methyllithium in ethers leads to decomposition. The compound is not deprotonated by KPH_2 in dimethyl ether.

Treatment of the *N*-methylpyridinium salt of $[Mo(CO)_5I]^-$ with phosphirane in CH_2Cl_2, however, gives the solid complex pentacarbonylphosphoranemolybdenum(0), $[(CH_2)_2PH]Mo(CO)_5$; the species $[(CH_2)_2PH]_2Mo(CO)_4$ and $[(CH_2)_2PH]_3Mo(CO)_3$ have been obtained from phosphirane and tetracarbonylnorbornadienemolybdenum or tricarbonylcyclohexatrienemolybdenum. The complexes have been characterized spectroscopically and by analysis, and the ^1H and ^{31}P-NMR spectra of $[(CH_2)_2PH]Mo(CO)_5$ have been obtained and analyzed, as have those of phosphirane itself[2].

The ^{31}P-NMR spectra are essentially first order, with $J(PH)$ equal to 333 Hz in the complex, compared with 155 Hz in phosphirane; the values obtained from the ^1H-NMR spectra are 330.2 Hz and 157.7 Hz, respectively. The magnitudes of the two couplings $J(HCP)$ have been obtained from the ^{31}P spectra, but the signs and magnitudes are found in the full analysis of the ^1H spectra. The values of $+2.2$ and -8.8 Hz for the complex compare with those of $+16.5$ and -2.2 Hz for free phosphirane. The only other couplings to change significantly on complexing are the two couplings $J(HCPH)$.

Pentacarbonylphosphiranemolybdenum reacts with KPH_2 in dimethyl ether, with liberation of 80% of the phosphane expected for the reaction:

$$[(CH_2)_2PH]Mo(CO)_5 + PH_2^- \longrightarrow [(CH_2)_2PMo(CO)_5]^- + PH_3$$

The resulting yellow salt reacts with trimethylchlorosilane with precipitation of a white solid; the IR, NMR, and mass spectra of the soluble products indicate the formation of the complex $[(CH_2)_2PSiMe_3]Mo(CO)_5$. There is a similar reaction with monobromosilane.

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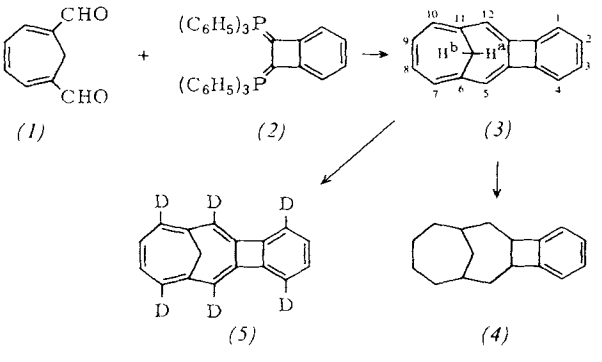
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6,11-Methanocyclobutabenzo[1,2-*a*][10]-annulene, a Biphenylene Analog Containing a Carbocyclic 10π-Electron Ring

By *P. J. Garratt* and *K. Peter C. Vollhardt*[*]

Biphenylene is one of the few examples of a polycyclic system composed of planar $4n$ and $(4n+2)$ π-electron rings, and as such has considerable theoretical interest[1,2]. The replacement of one of the benzene rings by a charged[3] or heterocyclic[4] 6 π-electron system has recently been reported, but no compounds are known in which a ring has been replaced by an annulene containing ten or more π-electrons[5]. We now report the synthesis of 6,11-methanocyclobutabenzo[1,2-*a*][10]annulene *(3)*, a compound formally derived from biphenylene by replacement of a benzene ring by 1,6-methano[10]annulene[6].



(1) *(2)* *(3)* *(5)* *(4)*

The addition of a solution of 1,3,5-cycloheptatriene-1,6-dicarboxaldehyde *(1)*[7] in THF to an equimolar solution of preformed 1,2-dihydro-1,2-bis(triphenylphosphoranylidene)-cyclobutabenzene *(2)*[8] in ether : benzene (3 : 1) at room temperature under nitrogen led to an immediate discharge of the red color and the formation after several minutes of a dark green mixture. After stirring for 2 hours, chromatography on alumina and subsequent preparative thin-layer chromatography on silica of the hydrocarbon fraction gave *(3)* as yellow crystals, mp 166–167° C, in 1% yield.

The structure is based on the molecular formula (*m/e* 216), and the spectral and chemical properties; electronic spectrum: (C_2H_5OH) λ_{max} = 223 (ε 15200), 280 (53600), 320 (31200), 388 (2800), and 398 nm (2800). This spectrum resembles that of 1,6-methano[10]annulene[6], except that the maxima are increased to longer wavelength and differ in relative intensity. The NMR spectrum (CCl_4, 100 MHz) has signals centered at τ = 3.06 (2H) and 3.30 (8H), and an AB-system at τ = 7.55 and 9.71 (*J* = 10 Hz).

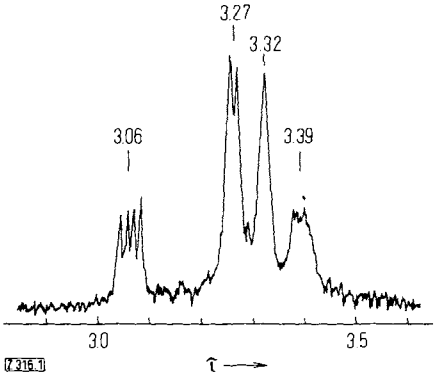


Fig. 1. The low field region of the 220 MHz NMR spectrum of *(3)* in CCl_4.

The low field region of the 220 MHz NMR spectrum of *(3)* is shown in the Figure [an AA'BB' system at τ = 3.06 and τ = 3.39 (H^8, H^9 and H^7, H^{10} respectively), an AA'BB' multiplet at τ = 3.27 (H^1–H^4), and a 2-H pseudosinglet at τ = 3.32 (H^5, H^{12})]. Irradiation (100 MHz) of the AB-signal at τ = 9.71 causes the pseudosinglet to sharpen, and irradiation of the AB-signal at τ=7.55 causes a change in the signals due to H^7, H^{10}. Since it is known that in 1,6-methano[10]annulenes the ring protons are more strongly coupled to the methylene proton which has the *anti*-orientation[9], the signal at τ=7.55 is attributed to H^a and that at τ=9.71 to H^b.

Hydrogenation of *(3)* over Pd/C in ethyl acetate gave the decahydro derivative *(4)* as a liquid.

The assignments of the ring protons are further supported by deuteration studies[6]. Treatment of *(3)* with CF_3CO_2D/D_2SO_4 in ether caused the disappearance of the proton signals in the order τ = 3.39, 3.32, and 3.27; the hexadeuterio compound *(5)* is eventually formed, which in the NMR spectrum has two singlets at τ=3.06 and 3.27 (1:1).

The positions of the ^1H and ^{13}C-NMR signals in biphenylene[2] and the ^1H-NMR signals in cyclobutabenzo[1,2-*c*]thiophene[4] have been attributed to the shielding effect of a paramagnetic ring current arising from the $4n$ π-electron 4-membered ring. The benzene protons in *(3)* show an upfield shift when compared to those in *(4)*, indicating that *(3)* also exhibits a paramagnetic effect. The chemical shift of the H^a methylene proton, at unusually low field for a delocalized bridged [10]annulene system[6,10], suggests that this proton is experiencing *paramagnetic deshielding* and must occupy a position inside the deshielding cone of the 4-membered ring.

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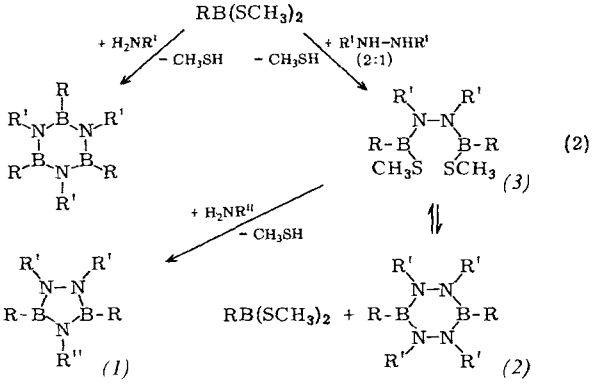
Derivatives of 1,3,4,2,5-Triazadiborolidine

By *Dieter Nölle* and *Heinrich Nöth*[*]

1,3,4,2,5-Triazadiborolidine *(1a)*, which is isoelectronic with cyclopentadiene, is unknown. Until now only two of its derivatives have been described, namely *(1b)*, which is formed on partial aminolysis of the corresponding 1,2,4,5,3,6-tetrazadiborine *(2)* with cyclohexylamine[1], and *(1c)*, which is formed from *N,N'*-dimethylhydrazine and $[(CH_3)_2N(C_6H_5)B]_2NH$[2]. We found the scope of both methods of preparation to be severely limited.

The fact that the equilibrium (1) can be shifted in favor of the BN compound opens up a new, simple route to compounds of type *(1)*. Although the diborylamine $[(CH_3)_2B]_2NH$ can be obtained from $(CH_3)_2BSCH_3$ and NH_3[3], reaction of 2 moles of $CH_3B(SCH_3)_2$ with 1 mole of NH_3 under mild conditions leads not to $[CH_3(CH_3S)B]_2NH$ but exclusively to the borazine $(CH_3BNH)_3$, which is obtained quantitatively when the reactants are used in the molar ratio 1:1[4]. This affords additional evidence for the kinetic instability of diborylamines of type $[R(X)B]_2NR'$[3]. On the other hand, reaction of 2 moles of $RB(SCH_3)_2$ with 1 mole of the hydrazines R'NH-NHR' under suitable conditions furnishes preferentially compounds of type *(3)* as well as *(2)* as a minor product. However, *(2)* is the major product when the reactants are present in a molar ratio of 1:1. Compound *(3)* readily reacts with NH_3 and primary amines to

$$\geq B\text{-}SR + H_2NR' \rightleftharpoons \geq B\text{-}NHR' + HSR \qquad (1)$$



(2)

give derivatives of *(1)*. It seems that the reaction also involves *(2)*, which appears to be in equilibrium with *(3)* according to Scheme (2), since *(2)* can no longer be detected by ^{11}B-NMR spectroscopy after reaction with the primary amine has reached completion. Small amounts of borazine derivatives are also formed [cf. Scheme (2)].

The method described above is suitable for the synthesis of many derivatives of *(1)* and of other boron heterocyclics[5].

	R	R'	R''	M.p. (°C)	B.p. (°C/torr)	δ^{11}B [a] (ppm)	Yield (%)
(1a)	H	H	H	-	-	-	-
(1b)	C_6H_5	CH_3	C_6H_{11}	101	-	-30.5	-
(1c)	C_6H_5	CH_3	H	110	-	-29.6	75
(1d)	CH_3	CH_3	H	37	93/130	-30.6	72
(1e)	CH_3	CH_3	CH_3	-	28/2.5	-31.8	63
(1f)	CH_3	CH_3	$N(CH_3)_2$	-	62/12	-31.0	60
(1g)	CH_3	C_6H_5	H	85	-	-34.4	70
(1h)	CH_3	C_6H_5	CH_3	88	-	-34.8	65

[a] Standard: $BF_3 \cdot O(C_2H_5)_2$, external.

Procedure:

A solution of *N,N'*-dimethylhydrazine (3 g) in diethyl ether (50 ml) is added during 24h to a stirred solution of $CH_3B(SCH_3)_2$ (13.2 g) in diethyl ether (40 ml) at 0 °C. If dry ammonia (1.27 g) is condensed into the solution at −70 °C a precipitate is formed that dissolves when warmed. Ether and methanethiol are then distilled off, first at 600 torr and finally at 400 torr, using a 50-cm spinning band column. Fractionation of the residue affords 2,4,6-trimethylborazine *(4)* (b.p. 58–68 °C/130 torr; 0.38 g), an intermediate fraction consisting of *(4)* and *(1d)*, and then *(1d)*, which suddenly solidifies to a mass of needle-shaped crystals.

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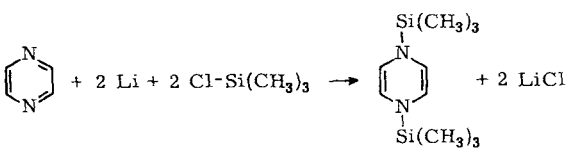
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1,4-Bis(trimethylsilyl)-1,4-dihydropyrazine by Reductive Silylation of Pyrazine

By *Reinhard A. Sulzbach* and *Abul F. M. Iqbal*[*]

The 1,4-dihydropyrazine system, which contains an interesting arrangement of two enamine structures, has hitherto received very little attention. This might be due to the lack of simple,



(1)

selective methods for synthesizing 1,4-dihydropyrazines. We have found that the 1,4-dihydropyrazine system can be prepared very easily by reductive silylation of pyrazine with alkali metals and halogenosilanes. Thus, if pyrazine is allowed to react with lithium and trimethylchlorosilane the yellow 1,4-bis(trimethylsilyl)-1,4-dihydropyrazine *(1)*, which is extremely sensitive to oxidation, is formed in almost quantitative yield.

Analogously to the reductive silylation of benzene[1] and pyridine[2] this reduction may proceed *via* radical anions of pyrazine.

Procedure:

A solution of pyrazine (20 g, 0.25 mole) in THF (75 ml) is added dropwise over a period of 1h at 0 °C to a mixture of lithium (5.2 g, 0.75 g-atom; particle size 1–10 μm), trimethylchlorosilane (81.5 g, 0.75 mole), and THF (75 ml). Unreacted lithium and precipitated lithium chloride are then filtered off. After removal of excess trimethylchlorosilane from the filtrate by distillation there remains a solid yellow residue. Recrystallization from diethyl ether yields *(1)* as yellow needles. Yield 50 g (88%); m. p. 65 °C; NMR: τ = 5.34 (H ring), 10.03 ($-CH_3$). Since *(1)* decomposes spontaneously in the presence of air all operations must be carried out in an inert atmosphere.

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The Thiazyl Cation $[NS]^+$

By *Oskar Glemser* and *Wolfgang Koch*[*]

Simultaneous introduction of sulfur nitride fluoride NSF (p = 1 torr) and the pentafluoride AsF_6 (p = 1 torr), or SbF_5 (p = 1 torr), into a quartz flask at room temperature[1] leads to products having the molecular composition $NSF \cdot XF_5$ (X = As or Sb), which according to spectroscopic findings, can be formulated as ionic compounds $[NS]^+[XF_6]^-$, *i.e.* as compounds containing the hitherto unknown thiazyl cation.

Proof of structure was afforded by the Raman spectrum of $[NS]^+[AsF_6]^-$, which exhibited the following bands (cm^{-1}; rel. intensity in brackets): 1437 (6), 684 (10), 557 (3), 368 (4). The bands at 684, 557, and 368 cm^{-1} can be assigned unequivocally to the $[AsF_6]^-$ ion: cf. *e.g.* $Cs[AsF_6]$[2]: $\tilde{\nu}_1$ 685, $\tilde{\nu}_2$ 576, $\tilde{\nu}_3$ 372 cm^{-1} and $[SF_3][AsF_6]$[3]: $\tilde{\nu}_1$ 676, $\tilde{\nu}_2$ 551, $\tilde{\nu}_3$ 366 cm^{-1}. The signal at 1437 cm^{-1} corresponds to the wave number of the NS vibration; as is to be expected it is higher than in the case of NSF ($\tilde{\nu}_{NS}$ = 1372 cm^{-1}). The same is true for the NS valence force constants[4] and NS bond orders[5] calculated from these results:

$f_{[NS]^+}$ = 11.85 mdynes/Å; bond order $N_{[NS]^+}$ = 2.6

$f_{NS}(NSF)$ = 10.71 mdynes/Å; bond order $N_{NS}(NSF)$ = 2.4

The ^{19}F-NMR spectra of the substances dissolved in AsF_6 confirm their ionic character: no SF signals appear between +350 and −440 ppm ($CFCl_3$ as external standard); exchange of fluorine between the anions and AsF_6 was not observed.

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Chromium Trichloride-Tris(aluminum trichloride)

By *Keith Lascelles* and *Harald Schäfer*[*]

We have observed that solid chromium(III) chloride can be chemically transported by gaseous aluminum(III) chloride in a temperature gradient (500 → 400 °C). There is therefore a reversible endothermic reaction by which the $CrCl_3$ is taken into the gas phase at 500 °C, and after an appropriate gas movement (diffusion, flow) is deposited again in the zone at 400 °C. An adequate concentration gradient of the chromium-containing molecule between the reaction spaces is necessary for a measurable transport effect. The equilibrium given in eq. (1) cannot be responsible since at 500 °C it still lies very much to the left; with $p(Al_2Cl_6) = 1$ atm, calculation gives $p(CrCl_4) \approx 10^{-11}$ atm[1,2].

$$4\ CrCl_{3,s} + Al_2Cl_{6,g} \rightleftarrows 4\ CrCl_{4,g} + 2\ AlCl_g \qquad (1)$$

On the basis of other known volatile $AlCl_3$ complexes $NaCl \cdot AlCl_3$[3,4], $CaCl_2 \cdot Al_2Cl_6$[5], $NdCl_3 \cdot 3\ AlCl_3$[6], $UCl_4\ 2\ AlCl_3$[7], and $UCl_5 \cdot AlCl_3$[7] we investigated the existence of a volatile compound of $CrCl_3$ and $AlCl_3$ responsible for the observed transport. In these experiments, carried out with the special exclusion of moisture, equilibrium spaces V_1 and V_2 were heated in metal block ovens at 400 and 500 °C respectively. They contained $CrCl_{3,s}$ and $Al_2Cl_6/AlCl_3$ and were connected by a diffusion path 80 mm long and 6 mm diameter. The same total pressure thus prevailed throughout the whole system. The partial pressures of Al_2Cl_6 and $AlCl_3$ in spaces V_1 and V_2 depended on the initial amount of $AlCl_3$ and the known dissociation equilibrium $Al_2Cl_6/AlCl_3$[2]. The partial pressure of $CrCl_3.x\ AlCl_3$ was neglected in the calculation of the total pressure.

In the range of measurements used, the total pressure Σp lay between 0.15 and 5.18 atm, the Al_2Cl_6 pressure in space V_2 between 0.067 and 4.49 atm, and the transport yield m/t between 10 and 84 mg $CrCl_3$/5 days. The analysis showed that the transport is caused by the formation of $(CrCl_3 \cdot 3\ AlCl_3)_g$ according to equilibrium (2):

$$CrCl_{3,s} + 1.5\ Al_2Cl_{6,g} \rightleftarrows (CrCl_3 \cdot 3\ AlCl_3)_g;\ Kp \qquad (2)$$

This conclusion was reached as follows:
The partial pressure of the initially unknown volatile chromium compound is represented as $p(Cr)$. The transport by diffusion between the equilibrium spaces V_2 and V_1 is, by the well-established relationships, proportional to $\Delta p(Cr) = p_2(Cr) - p_1(Cr)$, and inversely proportional to Σp[8]. It was found experimentally that $p_1(Cr) \ll p_2(Cr)$. The following is therefore true:

$$m/t \propto p_2(Cr)/\Sigma p$$

By introduction of the equilibrium constant for reaction (2), it follows that

$$m/t \propto p^{1.5}(Al_2Cl_6)/\Sigma p$$

The measured values were in good agreement with this relationship. Other formulas $CrCl_3 \cdot x\ AlCl_3$ with $x = 1$, 2 or 4 for the volatile complex are excluded unequivocally.

The *structure* of the compound $CrCl_3\ 3\ AlCl_3$ was not investigated, but a clear possibility is one in which the Cr is octahedrally, and the Al tetrahedrally surrounded by Cl. Such a molecule can exist in mirror isomerism.

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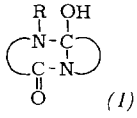
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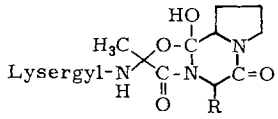
Synthesis of an Azacyclol[1][**]

By *Manfred Rothe, Tibor Tóth,* and *Dieter Jacob*[*]

Bicyclic, *N*-acylated orthodiamides containing a free OH group *(1)*, "azacyclols", are of interest as nitrogen analogs of the peptide part of the ergot alkaloids *(2)*. In addition they represent examples of the unstable tetrahedral intermediates in carbonyl reactions of acid amides with amines and amides, whose existence had hitherto been postulated only on the basis of the reaction kinetics.



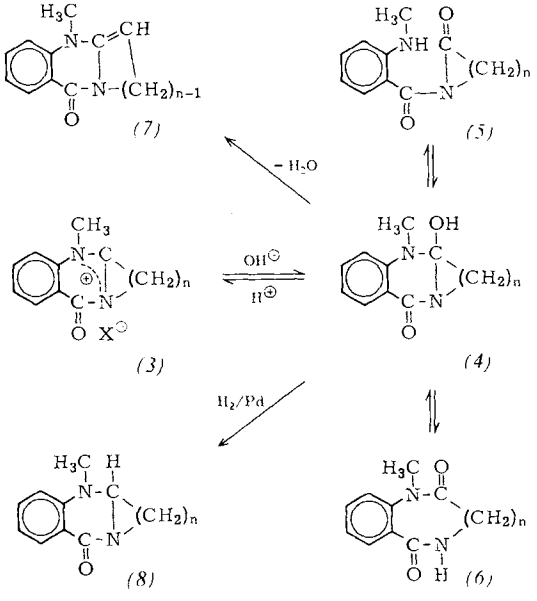
(1)



(2)

We have now synthesized a previously unknown type of azacyclol *(1)*. As in oxa-[2] and thia-cyclols[3] a fused benzene ring should increase the stability of the cyclol and render its unequivocal spectroscopic identification much easier.

The synthesis of the azacyclol *(4)*, $n = 3$, was accomplished by reaction of the acylamidinium salt *(3)* ($n = 3$, X = I) – which was prepared by *N*-methylation of 2,3-propano-4-quinazolone – with NaOH. In contrast to the representatives having a larger lactam ring[4], the azacyclol *(4)*, $n = 3$, is isolable and comparatively stable. Its structure was established unequivocally from elemental analysis, spectroscopic data, and from results of chemical reactions. The tautomeric structures *(5)* and *(6)* which have been taken into consideration as stabilization possibilities for cyclols – at least in equilibrium[2,3] – could be definitely ruled out.



(7) *(5)* *(3)* *(4)* *(8)* *(6)*

The UV spectrum with $\lambda_{max} = 223$ nm ($\varepsilon = 36500$) is in accord with the cyclol structure *(4)*, in contrast to the cyclodipeptide *(6)*, $n = 7$, which absorbs at $\lambda_{max} < 200$ nm. The structure *(5)* of the *N*-acylamides that absorb in the same region (*N*-benzoylpyrrolidinone: $\lambda_{max} = 228$ nm), could be ruled out on the basis

of the NMR spectrum (in [D_7]-DMF): The CH_3 signal would have to be split into a doublet by the NH proton, but only the singlet ($\tau = 6.87$ ppm) expected for *(4)* was found. Further characteristics are (i) the neighboring aromatic proton shifted downfield ($\tau = 2.18$ ppm) by the magnetic anisotropy of the carbonyl group, indicating coplanarity of the benzene ring and the heterocycle, and (ii) the OH signal occurring as a sharp singlet at $\tau = 6.68$ ppm (in [D_6]-DMSO) which establishes the presence of a tertiary OH group. In the IR spectrum the broad band at 3247 cm^{-1}, the unsplit carbonyl absorption (1631 cm^{-1}), and the very intense aromatic vibration at 1595 cm^{-1} give further evidence for the cyclol structure. In the mass spectrum the weak molecular peak at *m/e* 218 and the intense peak at M^+-18 [loss of water to give *(7)*] are also in complete agreement with this structure.

Chemical reactions affording proof of structure *(4)* are the formation of the acylamidinium salt *(3)* on treatment with dilute HCl, the catalytic hydrogenation to the deoxycyclol *(8)*[5], and the thermal elimination of water with formation of the anhydroazacyclol *(7)*, whose structure was deduced from the bromine addition reaction and from IR, UV, NMR, and mass spectra.

On attempting to synthesize the homologous azacyclol *(4)*, $n = 4$, from *(3)*, $n = 4$, by treatment with alkali, only the anhydroazacyclol *(7)*, $n = 4$, (m.p. 71 °C) could be isolated. Its structure was determined similarly to that of the cyclol; the olefinic double bond was established by IR ($\tilde{\nu} = 1656$ cm^{-1}) and NMR spectroscopy ($\tau = 6.11$ ppm, in $CDCl_3$). Both anhydroazacyclols are unstable and discolor on standing in air for a short time; this instability indicates their keteneaminal structure.

9a-Hydroxy-9-methyl-1H-2,3,3a,4,9,9a-hexahydropyrrolo-[2,1-b]quinazolin-4-one (azacyclol*(4)*, $n = 3$):

N NaOH (10.5 ml) is added dropwise with stirring over a period of 20 min to an ice-cold suspension of acylamidinium iodide *(3)*, $n = 3$, X = I, (3.28 g, 0.01 mole) in water (30 ml). The mixture is then stirred for an additional 30 min at 0 °C. The precipitate, which forms immediately, is filtered off, washed with ice-cold water (100 ml), and finally dried and stored in a refrigerator. Yield 1.71 g (79%), chromatographically pure, m.p. 91–92 °C.

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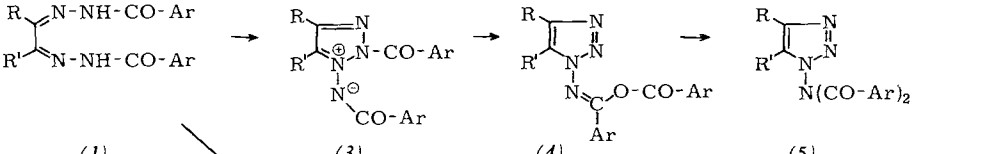
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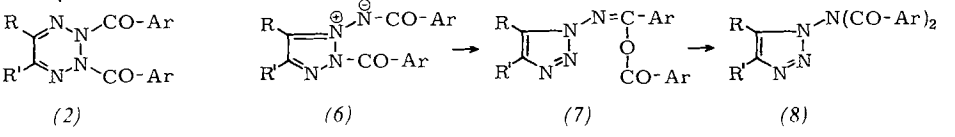
The Oxidation Products of Bisacylhydrazones of α,β-Diketones

By *Helmut Bauer, A. J. Boulton, W. Fedeli, A. R. Katritzky, A. Majid-Hamid, F. Mazza,* and *Alessandro Vaciago*[*]

Petersen and *Heitzer*[1] have recently "reinterpreted" the oxidations of the title compounds *(1)*, originally supposed[2] to give dihydrotetrazines *(2)*, as leading to "mesoionic"[3] triazoles *(3)*. As they appear to be unaware of the previous work, both by *Curtin* and *Alexandrou*[4–6] and by us[7,8] on this problem, and of the uncertainty which, despite this additional work, still surrounds the structure of these fascinating oxidation products, we feel that it is necessary to set the record straight so that further confusion may be avoided.



(1) *(3)* *(4)* *(5)*



(2) *(6)* *(7)* *(8)*

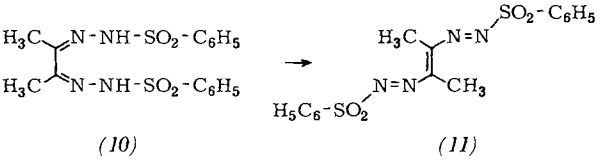
(a): R = R' = CH_3, Ar = C_6H_5
(b): R = H, R' = CH_3, Ar = C_6H_5
(c): R = CH_3, R' = C_2H_5, Ar = C_6H_5

It is clear that the known[2,4] conversion of the bishydrazones *(1)* into diacylaminotriazoles *(5)* involves two intermediates *(3)* and *(4)* of which only one can be isolated. Work by *Curtin* and *Alexandrou*[4] showed that the compound previously thought to be a dihydrotetrazine *(2)* was one of these intermediates, and they favored the structure *(4)*. Independent work by us[8] had led us initially to postulate the *N*-acylimide structure *(3)*. Unfortunately, despite much further work it is still not clear whether structures of type *(3)* or *(4)* are correct:

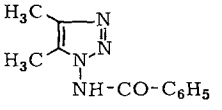
(i) Attempts to synthesize *(4a)* independently – by treating *(9)* successively with $SOCl_2$ and sodium benzoate – have so far failed.

(ii) The coupling constant of the methyl protons to the triazole ring protons in the ^{1}H-NMR spectrum of *(5b)* was the same (0.8 Hz) as that in the spectrum of the isolated intermediate, which favors structure *(4b)* with a similar 4,5-bond order, but is not conclusive.

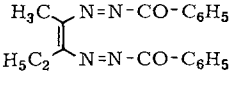
(iii) We found that the sulfonylhydrazone *(10)* was oxidized to a true bisazo compound *(11)*: this again tends to favor structures of type *(4)* over *(3)* for the acyl analogs since the sulfonyl derivative could give a compound analogous to *(3)* but not to *(4)*. On the other hand, cyano compounds with structures analogous to *(3)* are known in the bicyclic series[9].



(10) *(11)*



(9)



(12)

(iv) Oxidation of the unsymmetrical bishydrazone *(1c)* gave two products. Had they possessed structures *(3c)* and *(6c)* it might have been possible to interconvert them *via (12)* (cf. the corresponding interconversion of furoxanes[10]). However, each of these isomers is converted thermally only to the corresponding *(5c)* or *(8c)*: again negative evidence for the isolable intermediates existing as *(4c)* and *(7c)*.

(v) Infrared and ultraviolet spectra[4,5,11] and mass spectra[6] are not conclusive but, on the whole, favor the formulation *(4)*.

(vi) The obvious solution is to use X-ray crystallography. We prepared[7] the *para*-chloro-, *meta*-chloro-, *para*-bromo- and *meta*-bromo-substituted compounds *(3)* or *(4)* for this purpose, but unfortunately each one crystallized in a manner which made it unsuitable for X-ray examination[12]. We are at present trying to solve the more difficult problem of X-ray analysis of the parent compound *(3a)* or *(4a)* without a "heavy" atom.

We conclude that the problem of the structure of these oxidation products is as yet unsolved, although the balance of evidence at present favors the "amidotriazole enol ester" structure of type *(4)*.

Addendum: The X-ray analysis referred to in (vi) above has now been completed (December 15, 1970); the results confirm that the isolable intermediate of the conversion of the bishydrazones *(1)* into diacylaminotriazoles *(5)* has the "amidotriazole enol ester" structure *(4)*.

Compound *(4a)* crystallizes in the monoclinic system, space group $P2_1/c$, $a = 5.94$, $b = 10.76$, $c = 27.31$ Å, $\beta = 100.8°$, $Z = 4$.

The structure was solved by direct methods and refined to a current R value of 0.10, using 1576 independent reflections estimated visually from Weissenberg photographic records. The standard deviations of the bond lengths and bond angles, which define structure *(4a)*, are 0.01 Å and 0.6° respectively.

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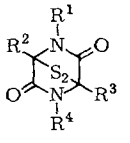
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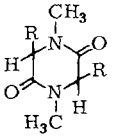
Synthesis of 2,5-Piperazinediones Having Sulfur-Containing Bridges between C-3 and C-6[**]

By *Hans Poisel* and *Ulrich Schmidt*[*]

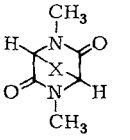
Gliotoxin[1], the virus inhibiting antibiotics of the aranotin type[2], the physiologically highly active sporidesmins[3], and the cancerostatic antibiotic chaetocin[4] all contain a 2,5-piperazinedione ring with a 3,6-epidithio bridge *(1)* as characteristic structural unit. One of the aims of our synthesis carried out in this series has been the direct introduction of sulfur functions into the 2,5-piperazinedione ring by nucleophilic substitution.



(1)



(2), R = Br
(3), R = SCH_3
(4), R = SH



(5), X = S_4
(6), X = S-C(S)-S
(7), X = S-C(O)-S
(8), X = S_2

	Mass spectrum	*m/e*	I_{rel}(%)	^{1}H-NMR δ (ppm) [a]
cis-(3)				2.38s (6) 3.09s (6) [b] 4.60s (2)
trans-(3)				2.06s (6) 3.10s (6) [b] 4.86s (2)
(5)	M^+	268	4	3.22s (6) 5.60s (2) [c]
	$(M-S_1)^+$	236	2	
	$(M-S_2)^+$	204	4	
	$(M-S_3)^+$	172	30	
	$(M-S_4)^+$	140	100	
(6)	M^+	248	31	
	$(M-CS_2)^+$	172	2.5	
	$(M-CS_3)^+$	140	100	
(7)				3.04s (6) 6.16s (2) [d]
(8)	M^+	204	9	3.12s (6) 5.24s (2) [b]
	$(M-S_2)^+$	140	100	
	$(M-S_2-CO)^+$	112	37	

[a] Against TMS as internal standard. [b] In $CDCl_3$. [c] In CF_3COOH. [d] In $(CD_3)_2SO$.

Treatment of 3,6-dibromo-1,4-dimethyl-2,5-piperazinedione *(2)* with methanolic methanethiolate solution leads to rapid formation of a *cis-trans* mixture of the dimethylthio compound *(3)*. Treatment with ethanethiolate leads exclusively to one isomer. Stereospecific introduction of *cis* sulfur functions into the 3,6-positions is achieved by reactions with dianions *via* bridge formation; thus, reaction of *(2)* with sodium trithiocarbonate *(6)* and with sodium tetrasulfide leads to the very stable compound *(5)* (in the model the diketopiperazine nucleus is planar and all interplanar angles in the tetrasulfide bridge are *ca.* 90°) in 67% yield. The tetrasulfide *(5)* can be reduced with sodium tetrahydridoborate to the *cis*-dithiol *(4)*, which, on treatment with S_2Cl_2 in absence of base regenerates the tetrasulfide *(5)* and on reaction with phosgene gives the dithiocarbonate *(7)* that can also be obtained by reaction of the trithiocarbonate *(6)* with mercuric acetate.

Trown has reported on the preparation of the dithiol *(4)* by reaction of the dibromide *(2)* with potassium monothioacetate followed by hydrolysis of the bis(monothioacetate)[5]. We have not been able to reproduce the dehydrogenation of the dithiol *(4)* to the epidithio compound (72% yield) with 3,3'-dinitro-5,5'-dithiodibenzoic acid reported by this author[6]. Under such conditions we have obtained only small amounts of a reaction product consisting primarily of the tetrasulfide *(5)*, a little epidithio compound, and some unknown reaction products.

Dehydrogenation of *(4)* with Fe^{3+}/O_2 leads to a crystalline oligomeric disulfide whose molecular weight cannot be determined osmometrically or mass spectrometrically. For the recording of its mass spectrum an inlet temperature of 100° C is necessary and decomposition (formation of S_8) occasionally takes place at the same time. The 20 eV spectrum affords evidence of a depolymerization to the epidithio compound. The epidithio compound *(8)* occurs in good yield and high purity in the dehydrogenation of the dithiol *(4)* in a two-phase system (dithiol in chloroform/aqueous KI_3 solution). The mass spectrum can be recorded at 30° C. 1,4-Dimethyl-3,6-epidithio-2,5-piperazinedione *(8)* is purified by high-vacuum sublimation and recrystallization. Its structure is confirmed by mass spectroscopy, vapor pressure-osmometric molecular weight determination, and NMR spectroscopy.

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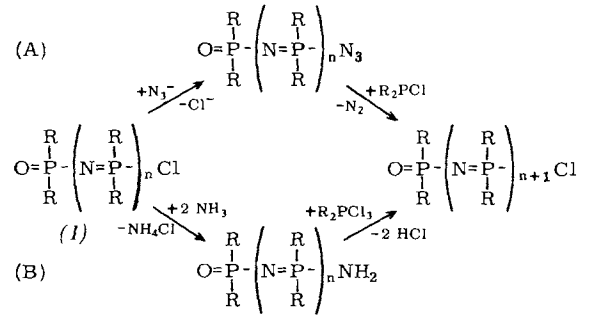
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[6] In Ref. [5] only the NMR spectra for *(2)* and *(4)* are given and not that for the epidithio compound *(8).* A signal at *m/e* = 204 [corresponding to the molecular ion of *(8)*] and the base peak M–S_2 (*m/e* = 140), which are the only characteristics quoted other than the decomposition point, are also observable in the spectra of the tetrasulfide *(5)* and the oligomeric sulfide *(vide supra).*

Cycloisomerization of Tetraphosphorus Nitride Oxide Derivatives: Octaphenyloxatriazatetra-P^V-phosphocinium Salts[1]

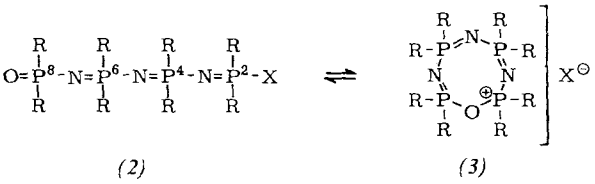
By *Alfred Schmidpeter* and *Karl Stoll*[*]

The routes (A) and (B) offer themselves for the formation and the stepwise extension of the chain of a phosphorus nitride oxide chloride:



Attempted use of route (A) for $n = 0$ (in this and in the following examples, R = C_6H_5)[2] led not to *(1)*, $n = 1$, but to a compound corresponding to *(1)*, $n = 3$, in its composition, and which was also designated as such[2], as major product. Meanwhile we have prepared *(1)*, $n = 1$, by another method and used it for route (B); surprisingly, the second step again gave a product whose analysis and properties agree with those of the compound described by *Paciorek*[2]. It is characterized by a very high melting point and a low solubility in nonpolar solvents.

While the favored formation of the P_4 chain *via* both routes (A) and (B) is striking and the properties of the product are unusual for a compound of type *(1)*, they are readily explained in terms of cyclic ionic isomers and by the justifiable assumption that in the case of $n = 3$, *i. e.* for the eight-membered ring *(3)*, X = Cl, the cyclic form will be particularly stable.



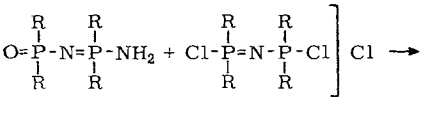
(2) *(3)*

The ^{31}P-NMR spectrum of $(R_2P)_4N_3OCl$ shows only two signals of equal intensity, thus confirming a high symmetry which is consistent only with the cyclic form. Moreover, the ionic structure is also apparent from the fact that the chlorine can be replaced by another anion (with $NaB(C_6H_5)_4$, $(C_5H_5N)_2AgClO_4$, $AgSbF_6$)[3] or incorporated into a chloro anion (with $SbCl_5$) without causing any change in the IR and ^{31}P-NMR spectrum of the rest of the molecule, *i.e.* of the cation (see Table).

In contrast, more powerful nucleophiles replace the chloride ion with concomitant ring cleavage; ammonia, monomethylamine, and diethylamine afford compounds *(2)*, X = NH_2, $NHCH_3$, and $N(CH_3)_2$, respectively, which unlike *(3)* melt at low temperatures and are readily soluble in benzene. Each one of the four phosphorus atoms gives rise to a signal whose shift is dependent upon X; the sum of the shifts amounts to -27 ± 1.7 ppm which is much higher than in the case of the ring compound (approx. –75 ppm). The azide and phenoxide[2] also appear to be represented by the covalent formula *(2)*, X = N_3, OC_6H_5. Hydrolysis of *(3)*, X = Cl, gives *(2)*, X = OH.

The cation in *(3)* is the first representative ($n = 3$) of a series $[(R_2P)_{n+1}N_nO]^+$ that is isosteric with the cyclophosphazenes. A phosphorus nitride oxide cation containing a six-membered ring has previously been formulated as a reaction intermediate[8].

Compound *(3)*, X = Cl, is best prepared by reaction of the amide of tetraphenylimidodiphosphinic acid with its trichloride:



2 HCl + *(3)*, X = Cl

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Equimolar amounts of the components react in boiling tetrachloroethane within about 8 h. When the solvent is distilled off there remains a paste-like residue which is extracted with boiling benzene. The product then crystallizes and can be recrystallized from nitromethane; yield *ca.* 50%.

Table. Chemical shifts $\delta^{31}P \times 10^6$ of octaphenyltetraphosphorus nitride oxide derivatives. (Positive values signify that the signals appear upfield from H_3PO_4.)

	X	M.p. (°C)	P^2+P^8		P^4+P^6		Solvent
(3)	Cl	339-340 (338-345 [2])	−25.7		−11.5		CH_2Cl_2
(3)	BPh_4	202-204	−25.4		−11.6		CH_2Cl_2
(3)	ClO_4	303-305	−25.7		−11.3		CH_2Cl_2
(3)	SbF_6	285-290	−25.0		−10.4		CH_3NO_2
(3)	$SbCl_6$	308-313	−27.6		−13.1		$C_2H_2Cl_4$
			P^2	P^4	P^6	P^8	
(2)	NH_2	77-83	−15.2	−10.4	−1.0	+1.3	CH_2Cl_2
(2)	$NHCH_3$	171-175	−19.5	− 9.7	+0.2	+2.0	CH_2Cl_2
(2)	$N(CH_3)_2$	130-136	−22.5	− 6.5	+0.2		CH_2Cl_2

The NMR signals of *(3)* (Table) are assigned to the two halves of the ring on the basis of the following comparison of the ^{31}P shifts:

	Y = S	O	$N^{\oplus}_{1/2}$	
$Y=R_2P-N=R_2P-Y^{\ominus}$	−35.6[4]	−12.7[5]	−11.5	*(3)*, P^4+P^6
$Y=R_2P-O-R_2P=Y$	−79.3[6]	−33.1[7]	−25.7	*(3)*, P^2+P^8

In the case of *(2)* the assignment is based on the expectedly relatively low shielding of the amino-substituted P^2 atom, which decreases further on methylation, and its competition with the shielding of P^4, which is characteristic for PNP systems[4].

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New Preparation of Isocyanides[1][**]

By *Rolf Appel, Roland Kleinstück,* and *Klaus-Dieter Ziehn*[*]

Isocyanides can be obtained by elimination of water from monosubstituted formamides. According to *Ugi* and *Meyr*[2] phosphorus oxide trichloride has proved to be a most effective dehydrating agent for this reaction. It reacts rapidly in the presence of pyridine or potassium *tert*-butoxide to give good yields in some cases (25 to 95%).

In conjunction with our studies on the ternary system phosphane/CCl_4/ammonia derivatives we have now found that isocyanides *(1)* are formed very readily by the joint action of triphenylphosphane, CCl_4, and triethylamine on monosubstituted aliphatic and aromatic formamides:

$$R\text{-}NH\text{-}CHO + Ph_3P + CCl_4 + (C_2H_5)_3N \longrightarrow$$

$$R\text{-}\overset{\oplus}{N}\equiv\overset{\ominus}{C}: + Ph_3PO + HCCl_3 + [(C_2H_5)_3NH]\,Cl$$

(1)

Use of a 20% excess of triphenylphosphane gives an approximately 90% yield of isocyanide.

(1)	R	Solvent	B.p.(°C/torr)	Yield (%)	Light petroleum (bp., °C)
(a)	*n*-C_4H_9	CH_2Cl_2	119/760	90	35-50
(b)	C_6H_5	$ClCH_2CH_2Cl$	54/12	91	60-95
(c)	C_6H_5-CH_2	$HCCl_3$	90-92/10	89	60-95

The elimination of water proceeds stepwise. An adduct is formed initially from the phosphane and CCl_4 which, as in the corresponding synthesis of nitriles from carboxamides[3] and carbodiimides from urea[4], phosphorylates the formamide at the oxygen. Chloroform is first liberated and then HCl.

Experiments with formamides deuterated at the nitrogen showed that the proton of the chloroform comes exclusively from the N–H bond.

$$Ph_3P + CCl_4 \longrightarrow [Ph_3PCl]CCl_3 \xrightarrow{OCH\text{-}NH\text{-}R}$$

$$[Ph_3\overset{\oplus}{P}\text{-}O\text{-}CH{=}NR]\,Cl^{\ominus} + HCCl_3$$

$$[Ph_3\overset{\oplus}{P}\text{-}O\text{-}\overset{H}{C}{=}N\text{-}R]\,Cl \xrightarrow[-[(C_2H_5)_3NH]Cl]{+(C_2H_5)_3N} Ph_3PO + \overset{\ominus}{:}C{\equiv}\overset{\oplus}{N}\text{-}R$$

(1)

General procedure:

Equimolar amounts of monosubstituted formamide, carbon tetrachloride, triethylamine, and triphenylphosphane (20% excess) are dissolved in 1,2-dichloroethane, dichloromethane, or chloroform (0.1 mole in 100 ml of solvent) and heated to 60 °C for 2.5 h. The solvent is distilled off at slightly reduced pressure and the residue is extracted five times with light petroleum. The residue left on removal of the light petroleum is then fractionated.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

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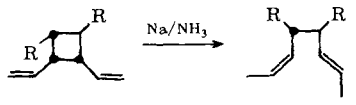
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Stereoelectronically Controlled Reductive Ring Cleavage of *cis*-1,2-Divinylcyclobutanes

By *Hansjörg Hey*[*]

Reduction of *cis*-1,2-divinylcyclobutane *(1a)*[1], which is readily accessible *via* a catalytic reaction, with alkali metals in liquid ammonia results in ring cleavage to give *cis,trans*-2,6-octadiene *(2a)* in 69% yield. The *trans,trans* isomer is formed in only 5.7% yield and the *cis,cis* isomer in 4.6% yield.

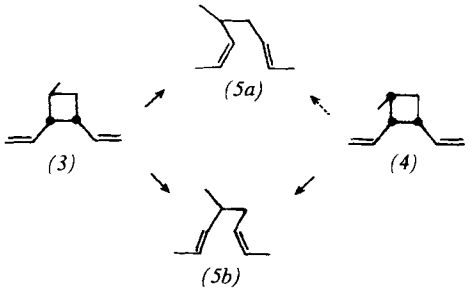


(1a), R = H *(2a)*, R = H
(1b), R = CH_3 *(2b)*, R = CH_3

Reduction of dimethyldivinylcyclobutane *(1b)*[2] under the same conditions gives 4,5-dimethyl-*cis,trans*-2,6-octadiene *(2b)* in 72% yield.

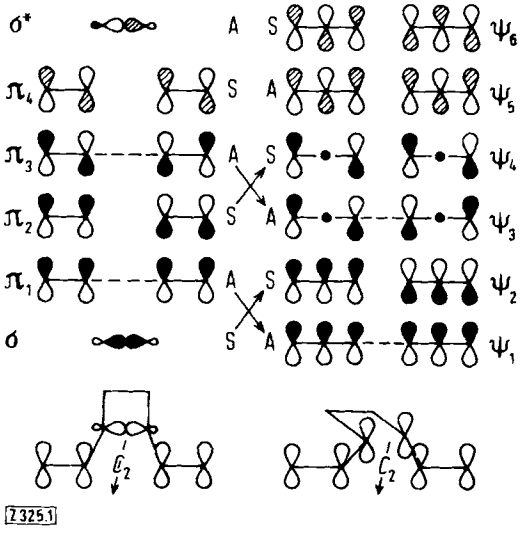
The reduction of the two isomeric 3-methyl-*cis*-1,2-divinylcyclobutanes *(3)* and *(4)*[3] yields different products for steric reasons. The *trans*-3-methyl compound *(3)* affords both possible methyloctadienes *(5a)* and *(5b)* as an approximately 1 : 1 mixture in an overall yield of 73%. However, compound *(4)* gives a 1 : 4 mixture of *(5a)* and *(5b)* in 81% yield.

The structures of *(2a)* and *(2b)* were assigned on the basis of the IR and ^{1}H-NMR spectra. In the case of *(5a)* and *(5b)* the structures were determined from the spectra and the retention behavior. The retention times are characteristic of allyl-substituted *trans*- and *cis*-2-alkenes respectively[4].



The first step in the reduction of the divinylcyclobutanes probably involves radical anions whose radical part is also transformed to an anion in the next step. During reduction the four-membered rings undergo cleavage between C–1 and C–2 (cf. ref.[5]). The divinylcyclobutanes afford allyl anions which are then protonated in such a way that thermodynamically favorable compounds having disubstituted double bonds are formed.

The surprisingly high stereospecificity of the reaction becomes readily understandable when it is regarded as a stereoelectronically controlled process in which conrotatory ring opening forms two anions having a *cis*- and a *trans*-allyl group. Fig. 1 shows a correlation diagram for this process.



Z 325.1

Fig. 1. Correlation diagram for the conrotatory opening of *(1a)* to *(2a)*.

A total of four molecular orbitals of *cis*-1,2-divinylcyclobutane participate in the rearrangement. The symmetry properties of the molecular orbitals with regard to a twofold symmetry axis C_2 are shown in the diagram. C_2 passes through the molecule perpendicular to the reacting σ orbital and to the π orbitals and is conserved with respect to the molecular orbitals taking part in the reaction, as is required for a conrotatory process.

The examples studied cannot be classed as electrocyclic reactions since no rearrangement of a cyclic compound into its conjugated polyene isomer takes place. A formal similarity to, *e.g.*, conrotatory opening of *cis*-3,4-disubstituted cyclobutenes to give *cis, trans*-2,4-dienes[6,7] nevertheless exists. In both cases the σ bond participating in the reaction occurs in the four-membered ring and the uppermost occupied π orbitals are of the same symmetry. Steric effects also play a role in determining the absolute rotation on conrotatory opening of the substituted *cis*-1,2-divinylcyclobutanes *(3)* and *(4)*, thus leading to an unequal distribution of the isomers *(5a)* and *(5b)* on reductive ring cleavage.

General procedure:

cis-1,2-Divinylcyclobutane (11.9 g, 0.11 mole) is dissolved in a mixture of liquid ammonia (approx. 100 ml) and ether (10 ml), and sodium metal (6.3 g, 0.274 mole) is added to the solution. The resulting blue solution is allowed to react for about 4 h at −33 °C. After the ammonia has evaporated overnight through a reflux condenser cooled to −25 °C, 50 ml of pentane is added and the reaction mixture is filtered. The solvent is distilled off and the residue analyzed by gas chromatography.

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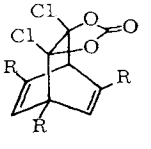
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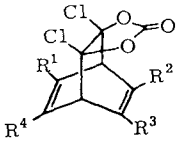
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Photochemical (2π+6π)-Cycloadditions. Novel 1,4-Cycloaddition with Formation of the Bicyclo-[2.2.2]octadiene System

By *Gerhard Hesse* and *Peter Lechtken*[*]

On irradiation with a high-pressure mercury vapor lamp[1] dichlorovinylene carbonate[2] adds to aromatic compounds if a Duran filter is used. The formation of a 1 : 1 adduct is established by elemental analysis and mass spectrometry. When benzene is used as substrate a molecular peak at *m/e* = 232 (Cl = 35) is obtained resembling a pattern typical of a dichloro compound. NMR and UV spectra show that the addition must have taken place in the 1,4 position.





(1a), R = H
(1b), R = CH_3

(2a), $R^1 = R^3 = H$; $R^2 = R^4 = CH_3$
(2b), $R^1 = R^2 = R^3 = R^4 = CH_3$
(2c), $R^1 = R^3 = H$; $R^2 = R^4 = OCH_3$

Cpd.	Rel. RR[a]	Quantum yield Abs. [b]	Rel.	M. p. (°C)	Yield (%) [c]
(1a)	1.00	0.007	1.00	116	11
(1b)	5.57	0.036	5.15	90	50
(2a)	1.89	0.011	1.57	117	44
(2b)	12.33	0.087	12.40	109	63
(2c)	5.25	0.038	5.43	99	42

[a] Reaction rate.
[b] Information regarding the irradiation performance of the TQ150 lamp as a function of wavelength and burning time was taken from the manufactures specifications. The quantum yields are valid for the first 100 mins' irradiation.
[c]Analytically pure product; referred to dichlorovinylene carbonate.

This 1,4 addition fits in with the series of 1,2 and 1,3 cycloadditions[3–5] found previously. The only example reported so far of a photochemical cycloaddition in the 1,4 position is the reaction of butadiene with benzene to give the bicyclo[4.2.2]-decatriene derivative[6], but only fair yields were obtained.

The 1,4 additions carried out by us by direct irradiation of *ca.* 10% solutions of dichlorovinylene carbonate in aromatic compounds gave relatively good yields and could be accelerated by a factor of about 40 by addition of acetone or acetophenone. A purely thermal addition to the hydrocarbon does not occur after 48 hours' heating at 150°C.

By way of example, proof for the structure of *(1b)* was obtained from the following data: NMR: τ = 4.40 (2 vinyl H/M); 6.28 (1 bridgehead H/T); 8.09, 8.11 (2 vinyl CH_3/D); 8.37 (1 bridgehead CH_3/S). UV: λ_{max} = 208 nm (ε = 1950). This absorption indicates unequivocally the presence of a bicyclo[2.2.2]octadiene system, for 1,3-cyclohexadiene absorbs at 258 nm (ε = 1600)[7] and values of 220 nm (ε = 3000) were found for 1,3 addition compounds[4]. The analogous norbornadiene, on the other hand, absorbs at 205 nm (ε = 2100)[8]. IR: the position of the carbonyl vibration at 1835 cm^{-1} indicates that the cyclic carbonate remained unchanged.

2,6-Dichloro-7,9,10-trimethyl-3,5-dioxatricyclo[5.2.2.$0^{2,6}$]-undeca-8,10-dien-4-one (1b)

Dichlorovinylene carbonate (8 g, 51.6 mmole) is dissolved under N_2 in anhydrous mesitylene (80 ml) and UV-pure acetone (10 ml) and then irradiated for 65 hours through a Duran filter. After removal of acetone and excess mesitylene a viscous oil is obtained which is then sublimed at 80–100°C/0.5 torr. The crystals thus obtained are pressed on an unglazed plate to remove any residual oil and recrystallized from petroleum ether. Yield 7.0 g (50%), m.p. 90°C, analytically pure.

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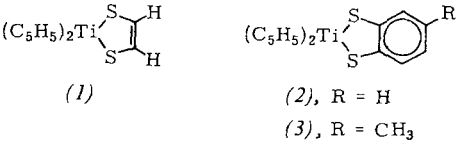
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Conformational Studies on Enedithiolate Chelates[**]

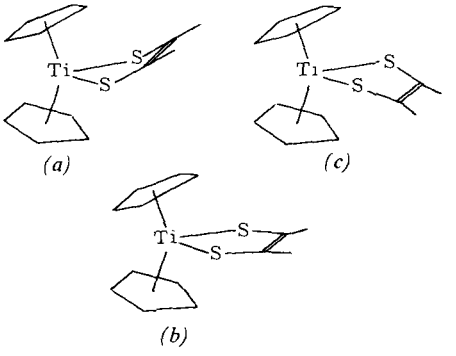
By *Hartmut Köpf*[*]

Although *cis*-1,2-enedithiolate (or α-dithiodiketone) complexes of transition metals nowadays number among the most thoroughly investigated *S*-coordinated chelate complexes[1] nothing has hitherto been reported regarding the possible conformations and inversion processes of the five-membered MS_2C_2 chelate rings in solution.

It is, however, to be expected that an insight into the spatial structure of metallocene enedithiolate chelates[2] will be provided by the ^{1}H-NMR spectrum of the cyclopentadienyl ligands, as in the case of metallocene polychalcogenide chelates[3]. In fact, the titanocene 1,2-enedithiolates *(1)*[4], *(2)*[5], and *(3)*[5]



(1) *(2)*, R = H *(3)*, R = CH_3



give spectra exhibiting a reversible temperature dependence of the C_5H_5 proton resonance[6], which is independent of the solvent and which is in the same sense for compounds *(1)*–*(3)*, while the signals of the groups C_2H_2, C_6H_4, and $C_6H_3CH_3$, respectively, remain unchanged in the temperature range studied. This observation can be interpreted in the following manner:

1) At −50°C the occurrence of two sharp singlets of equal intensity indicates the presence of the identical conformers *(a)* and *(c)* in which the magnetic equivalence of the two freely rotating cyclopentadienyl ligands of each molecule is canceled by a folding of the chelate rings along the S · · · S axis[7]. The nonplanar chelate rings are rigid; no measurable conformational transitions take place.

2) When the temperature of the sample is raised the signals broaden and finally coalesce between +10 and +20° C. This would indicate that the mutual interconversion *(a)*⇌*(c)* is now occurring at a detectable rate, probably *via (b)* as excited state[7]. The coalescence temperature T_c and the signal splitting $\Delta\nu$ afford the free energy of activation $\Delta G_c^{\neq}$ of this inversion process.

3) At normal measuring temperature (+36°C) a single sharp singlet appears, as would be expected for a rapid conformational

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[**] Metallocene enedithiolate chelates, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft. Ref. [2] is to be regarded as Part 1 of the series.

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interconversion of the now mobile, "dynamically planar" chelate rings.

For unbridged 1,2-enedithiolates containing no other kind of ligand attached to the central ion approximately planar chelate ring structures have been found in the solid state[1]; however, there are cases in which the ring is known to be folded[8]. The above results for solutions of *(1)–(3)* together with the analogous chelate ring folding in crystalline $(C_5H_5)_2MoS_2C_6H_4$[2] demonstrate that the planar structure *(b)* recently proposed[1] for metallocene enedithiolate chelates cannot be regarded as generally valid.

Cpd [a]	τC_5H_5 (ppm) [b]	$\Delta\nu$ (Hz) [c]	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mole^{-1})
(1)	3.94	22	+20	14.8
(2)	3.92	38	+10	14.0
(3)	4.10	38	+15	14.3

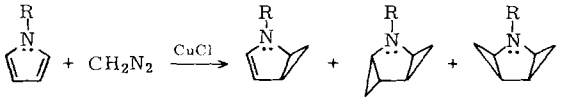
[a] In CS_2 solution. [b] Measuring temperature + 36 °C; TMS as external standard. [c] Measuring temperature −50 °C.

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Synthesis and Thermolysis of *N*-Methoxycarbonyl-2,3-homopyrrole[1,2]

By *Frank W. Fowler*[*]

We report that the cuprous chloride catalyzed decomposition of diazomethane in the presence of *N*-methoxycarbonylpyrrole produces mainly *N*-methoxycarbonyl-2,3-homopyrrole (*N*-methoxycarbonyl-2-azabicyclo[3.1.0]hex-3-ene) *(1)* in addition to smaller amounts of the bishomopyrroles *(2)* and *(3)* (3:1:0.6).

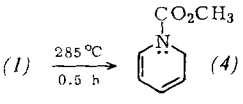


R = CO_2CH_3 *(1)* *(2)* *(3)*

The NMR spectrum ($CDCl_3$) of *(1)* shows τ = 3.60 (1H/broad,s), 4.53–4.70 (1H/m), 5.83–6.28 (1H/m), 6.22 (3H/s), 7.75–8.00 (1H/m), 8.98–9.37 (1H/m), and 9.83–10.08 (1H/m). This spectrum remains essentially unchanged from room temperature to 170 °C except that the vinylic hydrogen adjacent to the nitrogen atom appears as a doublet at high temperature and a broad singlet at room temperature. This observation is attributed to hindered rotation of the methoxycarbonyl group at room temperature.

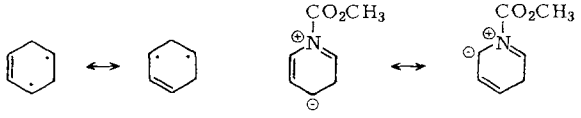
Previous studies have shown that the copper catalyzed decomposition of diazo compounds in the presence of pyrrole and its *N*-methyl derivative yields only substitution products[3] The formation of addition rather than substitution products with *N*-methoxycarbonylpyrrole is attributable to the known ability of the *N*-methoxycarbonyl group to cause pyrrole to behave as a diene[4].

Pyrolysis of *(1)* in the gas phase at 285 ° C produced a nearly quantitative yield of *N*-methoxycarbonyl-1,2-dihydropyridine *(4)*. The NMR spectrum ($CDCl_3$) is similar to that previously reported for *N*-phenyl-1,2-dihydropyridine[5]. Reduction of *(4)* ($LiAlH_4$) gives the known *N*-methyl derivative[6].



(1) *(4)*

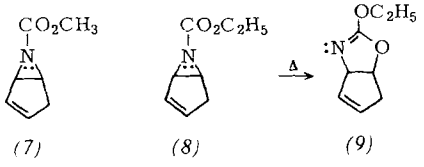
A comparison of the thermal isomerization of *(1)* with the carbocyclic analog indicates that the heterocycle rearranges more readily. Whereas the thermolysis of bicyclo[3.1.0]hex-2-ene to 1,3- and 1,4-cyclohexadiene has a half-life of 30 min at 339.4 °C[7] the isomerization of *(1)* proceeds to completion within 30 min at 285 °C. If a similar mechanism is assumed for the isomerization of *(1)* as has been proposed for bicyclo[3.1.0]hex-2-ene then the greater ease with which *(1)* rearranges is consistent with a greater stability of the delocalized intermediate *(6)* compared to the biradical *(5)*.



(5) *(6)*

Attempts to detect the aziridine *(7)* that should result from the presumably even more facile vinyl-cyclopropane rearrangement[8,10] have been unsuccessful. Carrying out the reaction at 245 ° C gave only a 30% conversion to the dihydropyridine *(4)*. No other product could be detected.

It is possible that aziridine *(7)* is thermally less stable than cyclopropane *(1)* and its equilibrium concentration is too small to detect. We believe this is unlikely and doubt that *(7)* is ever being formed. This conclusion is based on the known fact[9] that heating *(8)* gives the oxazoline *(9)* and neither the corresponding homopyrrole nor dihydropyridine. Orbital symmetry considerations also suggest that the interconversion of *(6)* with *(1)* should be more favorable than *(6)* with *(7)* which is consistent with our observations[11].



(7) *(8)* *(9)*

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[8] *W. v. E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat Edit. *2*, 115 (1963).

[9] *A. Mishra, S. N. Rice*, and *W. Lwowski*, J. Org. Chem. *33*, 481 (1968).

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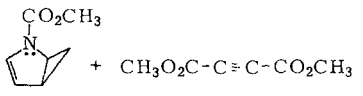
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Cycloadditions of *N*-Methoxycarbonyl-2,3-homopyrrole[1,2]

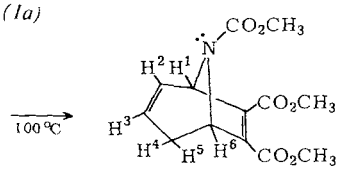
By *Frank W. Fowler*[*]

N-Methoxycarbonyl-2,3-homopyrrole (*N*-methoxycarbonyl-2-azabicyclo[3.1.0]hex-3-ene) *(1a)*[3] reacts with dimethyl acetylenedicarboxylate to give the cycloadduct *(2)*[4] [NMR

spectrum ($CDCl_3$): $\tau = 3.50 - 3.83$ (H^2/m), 4.25 – 4.61 (H^3/m), 4.90 (H^6/d, $J = 5.5$ Hz), 5.11 (H^1/d, $J = 5.0$ Hz), 6.18 (6 methyl-H/s), 6.27 (3 methyl-H/s), and 7.55 (H^4, H^5/center of broad AB)].



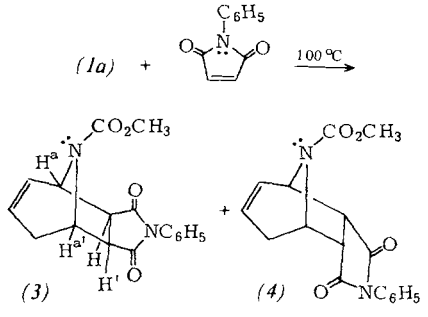
(1a)



(2a)

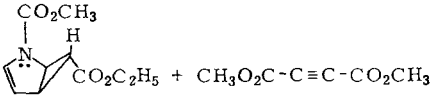
The above assignments were deduced from double resonance experiments. It is interesting to observe that H^6 occurs as a doublet suggesting zero coupling between H^6 and either H^4 or H^5. Dreiding molecular models and a comparison with the carbocyclic system[5] indicate that the bond to H^6 forms an angle of approximately 90° with the adjacent bond to the *endo* hydrogen. This would suggest that zero coupling occurs between H^6 and the *endo* hydrogen H^5.

N-Phenylmaleimide also reacts with *(1a)* to give two isomeric adducts in the ratio 2:3 which could be separated by preparative layer chromatography. The product *(3)* is assigned the *exo* configuration since the bridgehead hydrogens H and H′ appear as an AB pattern showing zero coupling to the bridgehead hydrogens H^a, and $H^{a'}$. Hydrogenation of *(3)* gives a symmetrical structure where the hydrogens that were responsible for the AB pattern now appear as a singlet. This result is consistent with the above assignment.

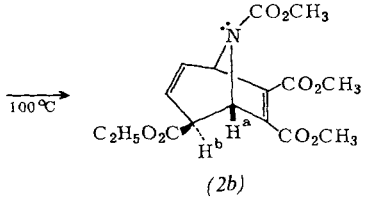


(3) *(4)*

The reaction of the homopyrrole with *N*-phenylmaleimide is first order with respect to both the homopyrrole and dienophile and shows almost no solvent dependence ($k_{CCl_4} = 1.36 \pm 0.11 \times 10^{-2}$ l mole^{-1}s^{-1} and $k_{CH_3C\equiv N} = 1.17 \pm 0.30 \times 10^{-2}$ l mole^{-1}s^{-1} at 75.08 °C).

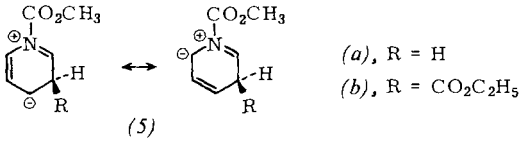


(1b)



(2b)

The reaction of DMAD with homopyrrole *(1b)*[6] follows an interesting course. There are two possible stereoisomers obtainable from this reaction. Only isomer *(2b)* is formed which readily rearranges on silica gel to the conjugated isomer. The stereochemical assignment of *(2b)* is based on the NMR spectrum. The bridge hydrogen H^a appears as a broad singlet indicating nearly zero coupling to the adjacent hydrogen H^b It follows from the above discussion that H^b must occupy the *endo* position.



(5)

These results can be explained in terms of dipole *(5)* which can be formed by a thermally allowed disrotatory ring opening of *(1)*. *(5b)* can undergo a 2+4 cycloaddition from the sterically unhindered side to give the observed product *(2b)*.

A concerted mechanism requires that the dienophile approach the homopyrrole from the *endo* direction. Molecular models indicate that electronically this type of attack is most favorable. That is, the cyclopropane bond that is being broken can be more nearly colinear with the p-orbital of the dienophile when attack occurs from the *endo* direction[7].

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[1] We are indebted to the National Science Foundation for partial support of this work.

[2] Presented by *F. W. Fowler* to the IUPAC Conference on Cycloaddition Reactions at München, September, 1970.

[3] *F. W. Fowler*, Angew. Chem. *83*, 147 (1971); Angew. Chem. internat. Edit. *10*, 135 (1971).

[4] This is formally a Diels-Alder reaction involving a homodiene. Previously, there has been reported only one example of this type of transformation; *S. Sarel* and *E. Brener*, J. Amer. Chem. Soc. *81*, 6522 (1959).

[5] *C. W. Jefford, B. Waegell*, and *K. Ramez*, J. Amer. Chem. Soc. *87*, 2191 (1965).

[6] *F. W. Fowler*, Chem. Commun. *1969*, 1359.

[7] The radical reactions of bicyclo[1.1.0]butane and bicyclo[2.1.0]-pentane with olefins also occurs from the *endo* direction. Electronically, these reactions are analogous and consistent with a concerted mechanism; *P. G. Gassman, K. T. Mansfield*, and *T. J. Murphy*, J. Amer. Chem. Soc. *91*, 1685 (1969); *M. Pomerantz, G. W. Gruber*, and *R. N. Wilke, ibid., 90*, 5040 (1968).

Hydrogendicarboxylate Ions as Hydrogen Bonded Chelate Systems in Organoantimony Compounds[1]

By *Hubert Schmidbaur* and *Karl-Heinz Mitschke*[*]

It was observed during systematic studies on the coordination chemistry of antimony in compounds of type R_4SbX[2] that the acceptor strength of the central atom is reduced considerably by the inductive effect of four organic groups R. Many of these compounds are consequently found to exist as monomeric, covalently bonded molecules; only in some cases are weak intermolecular interactions detectable and then only in the solid state (X = F, OH). Adducts of the type R_4SbXL in which L represents a monofunctional donor are largely unknown[3]. However, we have now found that a R_4SbXL adduct can exist when X and L are additionally linked by a *hydrogen bond*. We wish to report on the first representatives of this type of compound in the present communication.

The tetramethylantimony carboxylates *(1)*[4], which may be obtained from equimolar amounts of pentamethylantimony and a carboxylic acid R′COOH with elimination of methane, are volatile monomeric compounds containing pentacoordinated antimony: they are readily soluble in nonpolar solvents. Addition of a further mole of carboxylic acid leads to stable 1 : 1 adducts *(2)* which crystallize readily and whose acid content can easily be determined by titration. Elemental analysis provides confirmatory evidence for their composition. According to cryoscopic and ebullioscopic molecular weight determinations in benzene

the compounds *(2)* all exist in the form of monomers and, like *(1)*, they may therefore be regarded as molecular compounds.

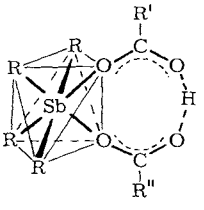
$$Sb \xrightarrow[-RH]{+R\,COOH} R_4SbOC(O)R' \xrightarrow{+R''COOH} R_4SbOC(O)R \quad R\,COOH$$

(1) *(2)*

$= CH_3$

The IR spectra of Nujol emulsions of *(2)* exhibit characteristic absorptions for the $(CH_3)_4Sb$ and R'COO moieties but none that can be attributed to a free hydroxyl group, thus indicating the presence of strong hydrogen bonds O...H–O. This assumption was confirmed by the highly informative ^{1}H-NMR spectra which exhibit, in addition to the $(CH_3)_4Sb$ singlet[5] and the signals due to two equivalent carboxylate groups, a sharp singlet in the extreme low-field region that is reserved for the resonances of strongly acidic hydrogens and those participating in hydrogen bonds (Table).

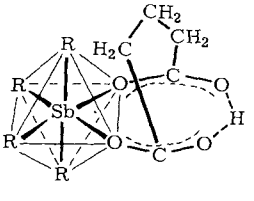
These findings are consistent only with the proposed structure *(3)* which provides the possibility of chelate interaction between the tetramethylstibonium ion and hydrogen bonded hydrogendicarboxylate ions. For steric reasons formation of a *cis*-chelate at the antimony atom is most likely. The gain in energy from the hydrogen bond on formation of an eight-membered ring system (without significant loss of entropy) adds to the small amount of energy resulting from the carboxylate coordination at the Sb atom thereby endowing the complex with sufficient stability[6].



(3)

In addition we were able to show that the eight-membered ring system can also be formed from two different carboxylic acids ($R' \neq R''$; $R' = CH_3$, $R'' = C_6H_5$).

It is apparent from a consideration of models that a linkage of the two carboxylic acids by way of their groups R' and R'' only becomes possible when the bridging chain of carbon atoms has reached a certain length. Thus reactions of $Sb(CH_3)_5$ with the *di*carboxylic acids oxalic acid, malonic acid, and succinic acid do not lead to products of low molecular weight; such a product is however obtained with *glutaric* acid. The resulting compound probably has the bridgehead structure *(4)* in which the bicyclic ring system is again closed *via* a hydrogen bond.



(4)

Table. Properties of compounds of type *(2)*, *(3)*, or *(4)*, respectively.

R	R'	R''	m.p. (°C)	NMR: τ(ppm), TMS, external ≙ 10 R	R' R''	H bond	solvent
CH_3	H	H	39	8.22	1.33 (s)	−6.25	CH_2Cl_2
CH_3	CH_3	CH_3	85-86	8.43	8.32 (s)	−4.31	CH_2Cl_2
C_6H_5	CH_3	CH_3	112-113	2.33	8.20 (s)	−1.50	CH_2Cl_2
CH_3	CH_3	C_6H_5	58-59	8.40	8.0 (s) | 2.3 (m)	−5.00	CH_2Cl_2
CH_3	C_6H_5	C_6H_5	80-81	8.40	2.3 (m)	−2.83	CH_2Cl_2
CH_3	$(CH_2)_3$		92-93	8.73	8.2 (m)	−4.90	CD_3CN

Molecular weight determinations, elemental analyses, and IR and NMR spectra again confirm the composition of the compound and the existence of the hydrogen bond. Corresponding structural features have meanwhile also been found in other organometallic systems.

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[1] Part 1 of a new series.

[2] *H. Schmidbaur, J. Weidlein, and K.-H. Mitschke,* Chem. Ber. *102*, 4136 (1969).

[3] Exceptions are encountered when XL is a 2,4-pentanedionate or quinolinate type of chelate: *H. A. Meinema, E. Rivarola,* and *J. G. Noltes,* J. Organometal. Chem. *17*, 71 (1969); *H. A. Meinema* and *J. G. Noltes, ibid. 16*, 257 (1969).

[4] *H. Schmidbaur, J. Weidlein,* and *K. H. Mitschke,* to be published.

[5] We attribute the equivalence of the four methyl groups on the octahedron to ligand reorganization (pseudorotation) processes.

[6] Carboxylic esters, which are unable to form hydrogen bonds, do not add to *(1)*.

Pentachalcogenide Chelates of Vanadium[**]

By *Hartmut Köpf, Alexander Wirl,* and *Werner Kahl*[*]

Metallocene polychalcogenide chelates having an element of subgroup IV[1] or subgroup VI[2,3] as central atom have already been reported. We have now been able to prepare the first polychalcogenide chelates of a subgroup V element[4] and, at the same time, the first paramagnetic complexes of this type, namely the pentachalcogenide six-membered ring chelates containing the d^1 central ion V^{IV}, $(C_5H_5)_2VS_5$ *(1)* and $(C_5H_5)_2VSe_5$ *(2)*. Their preparation was accomplished by reaction of dichlorobis-(π-cyclopentadienyl)vanadium(IV)[6] with ammonium pentasulfide and sodium pentaselenide in acetone respectively:

$$(C_5H_5)_2VCl_2 + M^I_2X_5 \longrightarrow (C_5H_5)_2V\begin{matrix}X\text{-}X\\ \diagup\quad\diagdown\\ X\quad\ X\\ \diagdown\quad\diagup\\ X\text{-}X\end{matrix} + 2\ M^ICl$$

(1), X = S
(2), X = Se

The black crystals of *(1)* and *(2)* are stable towards air (decomposition at 180 °C) and are soluble in all the usual organic solvents; however, the solutions of *(1)*, and in particular those of *(2)*, are rapidly decomposed by even a trace of atmospheric oxygen. Compounds *(1)* and *(2)* can be crystallized from dimethylformamide (DMF) in an inert atmosphere. The composition $(C_5H_5)_2VX_5$ was established by elemental analysis; the molecular weights determined cryoscopically in benzene show that *(1)* and *(2)* are also present in the monomeric chelate form in their solutions.

As derivatives of quadrivalent vanadium in solution (DMF), compounds *(1)* (*g*-value 1.976) and *(2)* (2.006) show, as they do in the solid state (see Figure), an intense ESR signal[7], while the C_5H_5-^{1}H-NMR signal (in DMF solution) remains absent.

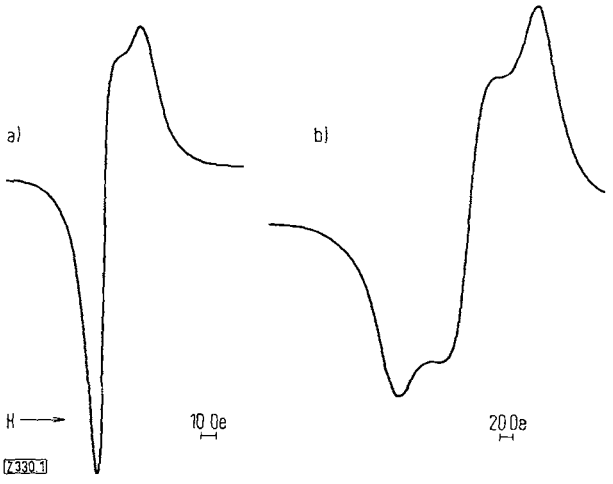


Fig. Solid-state ESR spectra of a) *(1)*, ampl. 1, and b) *(2)*, ampl. 8 at room temperature.

The IR spectra of *(1)* and *(2)* recorded on KBr disks are almost congruent with those of $(C_5H_5)_2TiX_5$[1] in the region where the vibrations of the π-C_5H_5 ligands occur. The S–S stretching mode of *(1)* appears, like that in $(C_5H_5)_2TiS_5$[1] and $[Pt(S_5)_3]^{2-}$[8], as a weak double band (478 and 455 cm^{-1}), while in five-membered chelate rings of type MS_4[2,3,9] it occurs as a single peak of medium intensity.

Bis(π-cyclopentadienyl)pentasulfidovanadium(IV) (1) and -pentaselenidovanadium(IV) (2):

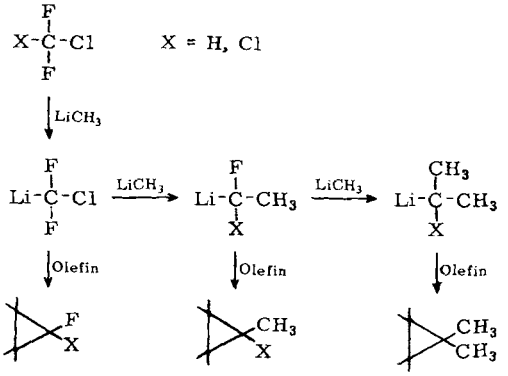
The preparation and all investigations of *(1)* and *(2)* in solution must be carried out in air-free solvents and in an argon atmosphere. For the preparation of $(NH_4)_2S_5$ and Na_2Se_5 solutions cf. Ref. [3]. – A suspension of $(C_5H_5)_2VCl_2$[6] (0.50 g, 2 mmoles) in acetone (20 ml) is poured with stirring into an aqueous solution (0.8 ml) of $(NH_4)_2S_5$ (2.5 mmoles/ml) or added dropwise to a solution of Na_2Se_5 (2 mmoles) in acetone (20 ml) and stirred for 2 h at 60 °C. After cooling the black precipitate is filtered off, washed with cold ethanol/water (3 : 1), and dried under vacuum. It is then dissolved in hot DMF (60 °C) and crystallized at −30 °C. Washing with cold absolute ethanol and drying under vacuum yields 0.51 g (74%) of *(1)* as black needles, or 0.18 g (16%) of *(2)* as a black crystalline powder respectively.

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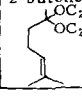
Alkyl/Halogen Substitution in Carbenes (Carbenoids): A Route to New Cyclopropane Derivatives[**]

By *Manfred Schlosser* and *Le Van Chau*[*]

Treatment of chlorodifluoromethane or dichlorodifluoromethane with methyllithium leads to formation of a short-lived intermediate (carbene, carbenoid, or carbenoid complex[1]), which reacts with olefins to give difluorocyclopropanes *(1)* and – to a lesser extent – chlorofluorocyclopropanes *(2)*. However, the intermediate chiefly reacts with further organometallic compound with replacement of one or two halogen atoms by methyl groups[2]. The 1-fluoro-1-methylcyclopropanes *(3)*, 1-chloro-1-methylcyclopropanes *(4)*, and the 1,1-dimethylcyclopropanes *(5)* can be isolated as final reaction products (see Table). The reaction scheme has been simplified as far as possible.



(1), X = F *(3)*, X = F *(syn+anti)* *(5)*
(2), X = Cl *(syn+anti)* *(4)*, X = Cl *(syn+anti)*

	Reaction conditions [a]	Olefin	Yields (%)					
			(1)	*(2)*	*(3)*	D-ratio [b]	*(4)*	*(5)*
$CHClF_2$	A, −78 °C	Cyclohexene	[c]	2	23	(2.7:1)	2	8
$CHClF_2$	B, −50 °C	Cyclohexene	[c]	< 1	8.3	(3.5:1)	1.5	4
CCl_2F_2	B, −50 °C	Cyclohexene	[c]	< 1	8.5	(3.5:1)	1.8	3.5
CCl_2F_2	B, −78 °C	Cyclohexene	[c]	< 1	8.5	(1.8:1)	3	2
CCl_2F_2	C, −78 °C	Cyclohexene	[c]	< 1	8	(2.2:1)	2	3
CCl_2F_2	B, −50 °C	2-Methyl-2-butene	9	–	15	(2.3:1)	1 [d]	2 [d]
CCl_2F_2	B, −50 °C		12 [e]	–	12 [e]	(1.5:1)	–	1

[a] See also the general procedure. Variants:
A: The methyllithium, after removal of as much ether as possible under vacuum, was suspended in cyclohexene and then treated with the halogenomethane; B: The ethereal methyllithium solution was added dropwise over a period of 2 h to the halogenomethane/olefin mixture; C: As in B, but duration of addition reduced to 5 min.

[b] D-ratio = ratio of diastereoisomers; presumably there is a preponderance of the diastereoisomer whose halogen atom takes up the *trans* position to the greater number of vicinal alkyl residues.

[c] No detectable amounts (<0.3%).

[d] Structural assignment on the basis of gas-chromatographic retention times only.

[e] Isolated as ketone after acid hydrolysis.

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[**] Organometallic Polychalcogenide Chelates, Part 5. This work was supported by the Deutsche Forschungsgemeinschaft. – Part 4: Ref. [3].

[1] *H. Köpf, B. Block,* and *M. Schmidt,* Chem. Ber. *101*, 272 (1968); *H. Köpf* and *B. Block, ibid. 102*, 1504 (1969); *H. Köpf, ibid. 102*, 1509 (1969).

[2] *H. Kopf,* Angew. Chem. *81*, 332 (1969); Angew. Chem. internat. Edit. *8*, 375 (1969).

[3] *H. Köpf, W. Kahl,* and *A. Wirl,* Angew. Chem. *82*, 814 (1970); Angew. Chem. internat. Edit. *9*, 801 (1970).

[4] The recently described compounds $(C_5H_5)_2Nb(S_2)X$ are to be regarded as π-complexes of the S_2 molecule [5].

[5] *P. M. Treichel* and *G. P. Werber,* J. Amer. Chem. Soc. *90*, 1753 (1968).

[6] *G. Wilkinson* and *J. M. Birmingham,* J. Amer. Chem. Soc. *76*, 4281 (1954).

[7] We are grateful to Dr. *D. Scheutzow* and Frl. *H. Feenders,* Universität Würzburg, for recording the ESR spectra.

[8] *A. E. Wickenden* and *R. A. Krause,* Inorg. Chem. *8*, 779 (1969).

[9] *J. Chatt* and *D. M. P. Mingos,* J. Chem. Soc. *A 1970*, 1243.

1-Butylfluorocyclopropanes are obtained analogously when *n*-butyllithium is used as metalating agent (*e.g.* 6% *syn*- and *anti*-7-butyl-7-fluoronorcarane from cyclohexane). With phenyllithium, only tetraphenylethylene was formed – presumably *via* α,α'-difluorostilbene. If, however, the stationary concentration of the organometallic compound is diminished by ate-complex formation with pentaphenylantimony[3], approximately 1% difluoronorcarane can be detected.

General procedure:

A solution of organolithium compound (0.20 mole) in petroleum ether or diethyl ether is added dropwise over a period of 15 minutes to a mixture of dichlorofluoromethane (or chlorodifluoromethane) (40 ml) and olefin which is kept at −40 to −50 °C. The reaction mixture is then allowed to warm to room temperature and the excess of halogenomethane allowed to evaporate. The mixture is hydrolyzed with dilute acid, washed, and dried. After evaporation of the lowest boiling constituents the mixture is fractionated, if necessary under vacuum, with a spinning band column. The reaction products usually have to be purified by gas chromatography.

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[**] Financial support by the Deutsche Forschungsgemeinschaft and gifts of chemicals by Farbwerke Hoechst are gratefully acknowledged.

[1] Cf. *U. Burger* and *R. Huisgen*, Tetrahedron Lett. *1970*, 3049, 3053, 3057; *L. Friedman, R. J. Honour*, and *J. G. Berger*, J. Amer. Chem. Soc. *92*, 4640 (1970); *M. Schlosser* and *G. Heinz*, Chem. Ber. *103*, 3543 (1970), and further literature cited there.

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[3] *G. Wittig* and *K. Clauss*, Liebigs Ann. Chem. *577*, 26 (1952); *G. Wittig* and *E. Benz*, Tetrahedron *10*, 37 (1960).

CONFERENCE REPORTS

Investigation of the Self-Diffusion of Small Molecules in a High-Molecular Environment

By *Robert Kosfeld*[*]

Self-diffusion is a translatory motion in which the molecules move in any direction with respect to their immediate environment in accord with statistical laws. This molecular-kinetic process depends on the intermolecular interactions between the molecules that determine the structure of the relevant system. The characteristic parameter of self-diffusion is the self-diffusion coefficient (SDC). Accurate knowledge of this coefficient as a function of the temperature, pressure, particle concentration of individual components, and the duration of measurement affords an insight into the structure of the system under investigation.

Particular interest attaches to the study of the translational motion of small molecules in a polymeric environment since both synthetic and biological polymers often contain components of low molecular weight (for example as plasticizers). Not only will the polymeric part of the system exert an effect on the mobility of the solvent molecules but the solvent molecules in turn will have a profound influence on the properties of the polymeric part of the system.

The spin-echo technique is well suited for the study of molecular-kinetic processes, and offers several distinct advantages over conventional methods for the determination of the SDC. Thus the molecules or even parts of molecules are labeled in that the relevant atoms acquire a certain phase difference with respect to one another. Compared with the tracer technique the system is far less perturbed; consequently the results obtained represent a better approximation to the processes occurring in the unperturbed system.

In multicomponent systems in which several self-diffusion processes are taking place the individual events can be detected simultaneously and independently of one another.

Whereas the usual spin-echo technique for determination of the SDC employs field gradients of the same sign that are either constant with respect to time or, as in the method devised by *Tanner* and *Stejskal*[1], applied as pulses, we have developed a method utilizing alternating field gradient pulses[2]. This technique permits determination of the SDC in the wide range between 10^{-10} and 10^{-3} cm^2s^{-1}. The shortest diffusion time measured so far with our apparatus is 80 μs. The minimum time that can be measured using field pulses of the same sign is about 2000 μs. The method has been used for diffusion-time dependent SDC measurements on the sintered glass membrane/benzene system and the effect of hindered diffusion has been studied more closely.

More attention was devoted to the study of the temperature dependence of the SDC of polystyrene (PST) in a solution containing 85.7 mole-% of deuterated benzene. Between 40 and 100 °C the diffusion process can be described by an Arrhenius equation with an activation energy of $\Delta E = 3.7$ kcal $mole^{-1}$. In the case of pure benzene the activation energy for the diffusion process was found to be $\Delta E = 3.0$ kcal $mole^{-1}$.

The temperature and concentration dependence of the SDC of benzene in crosslinked and non-crosslinked PST was the subject of a detailed investigation. An Arrhenius plot also gave a linear relationship for the SDC of benzene in both crosslinked and non-crosslinked PST. The activation energy increases with the polymer concentration from 3 kcal $mole^{-1}$ to 12 kcal $mole^{-1}$ in a system containing 25 wt.-% of benzene. The concentration dependence of the SDC of benzene above 60 wt.-% of benzene is described adequately by a simple exponential relation. Evaluation of the numerical results according to the Doolittle-Fujita theory[3] permits determination of the relative free effective volume f and the SDC D_{so} of pure PST:

T (°C)	30	40	50	60	70
$f \times 100$	5.9	6.1	9.5	7.9	7.9
D_{so} ($cm^2 s^{-1}$)	2.2×10^{-11}	4.6×10^{-11}	9.0×10^{-8}	1.8×10^{-9}	1.6×10^{-9}

T (°C)	80	90	100
$f \times 100$	8.6	9.6	10.1
D_{so} ($cm^2 s^{-1}$)	4.6×10^{-9}	2×10^{-8}	7.3×10^{-8}

Other authors[4] have obtained a value of 0.13 for the free volume from pressure- and temperature dependent volume meas-

urements at 90°C. In this case the free volume is regarded as the total volume less the volume of the molecules in closest packing. It should however be noted that an additional volume is taken up by intermolecular interactions between molecules of polymer and of benzene which is no longer available to the benzene molecules in the self-diffusion experiments. This would offer at least a qualitative explanation of the difference in the free volumes determined by the two methods.

In conclusion, attention is drawn to the fact that a "discontinuity" is observed at 50°C in the plot of the temperature dependence of the SDC of pure PST which can be attributed to rearrangement of the phenyl rings.

Lecture at Bochum on November 26, 1970 [VB 265 IE]
German version: Angew. Chemie *83*, 151 (1971)

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[1] *J. E. Tanner* and *E. O. Stejskal*, J. Chem. Phys. *42*, 288 (1965).

[2] *B. Gross* and *R. Kosfeld*, Messtechnik *7/8*, 171 (1969).

[3] *A. K. Doolittle* and *H. Fujita*, Advan. Polymer Sci. *3*, 1 (1961).

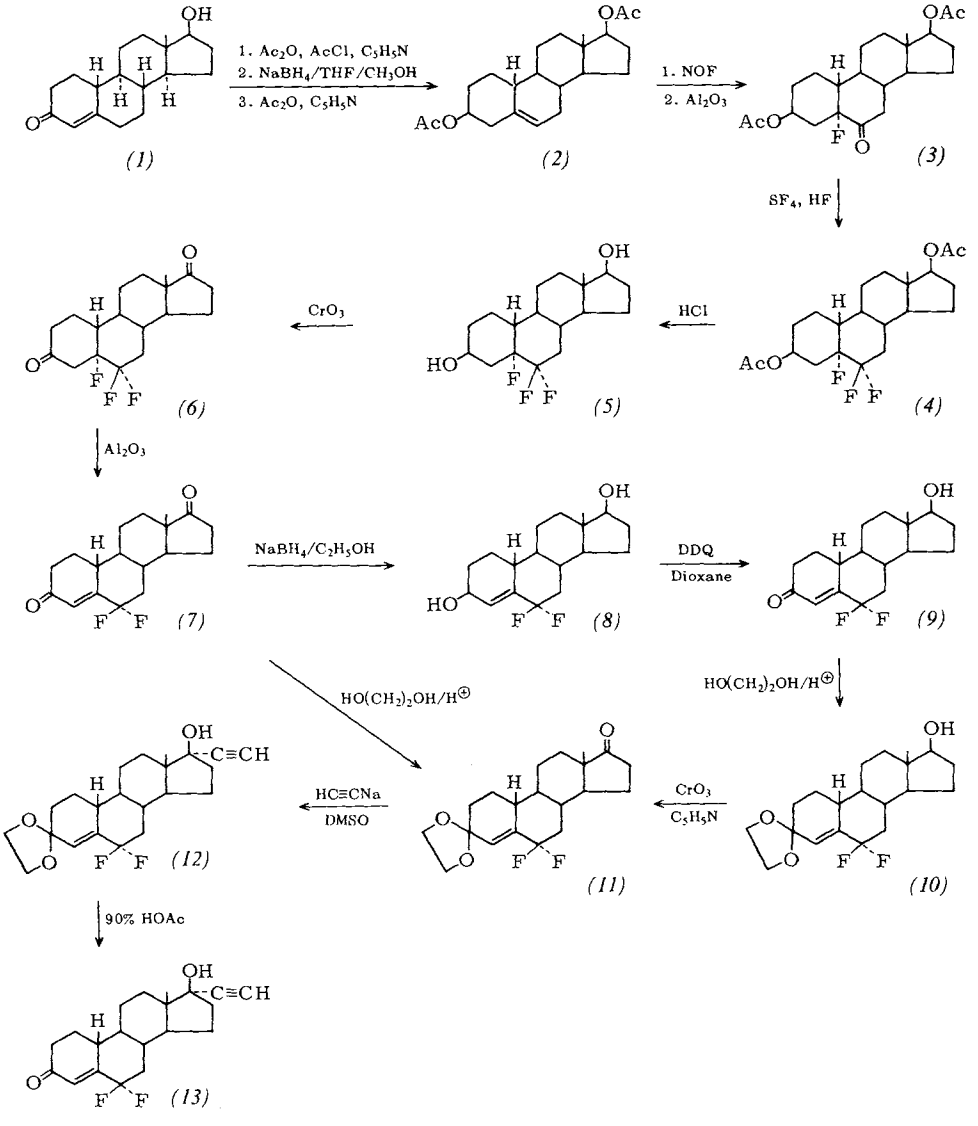
[4] *R. N. Haward*, *H. Breuer*, and *G. Rehage*, Polymer Lett. *4*, 375 (1966).

Synthesis, Chemistry, and Biological Properties of Some Novel Hormonal Fluorosteroids

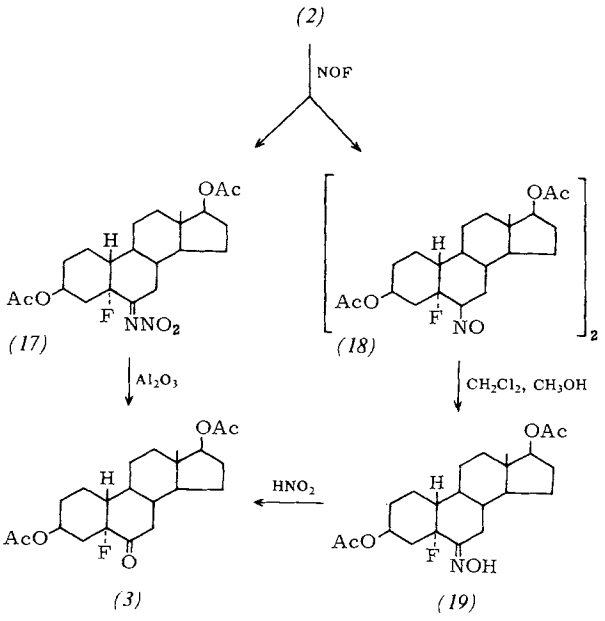
By *G. A. Boswell, Jr.* (Lecturer), *A. L. Johnson*, and *J. P. McDevitt*[*]

Previous investigations into the effect of 6,6-difluoro substitution of steroids on their hormonal activity showed that in certain progestational steroids activity was considerably enhanced[1]. It was of interest to establish if such a modification would increase the biological activity of the clinically important 17α-ethynyl-19-nortestosterone (norethindrone). Introduction of the two fluorine atoms onto C-6 of the 19-norsteroid nucleus was accomplished using nitrosyl fluoride and sulfur tetrafluoride as the key reagents (Schemes 1 and 2).

Treatment of 3β,17β-diacetoxy-5(6)-estrene *(2)* with NOF in CH_2Cl_2 gave a separable mixture of 3β, 17β-diacetoxy-5α-fluoro-6-nitroiminoestrane *(17)* and the dimer of the 5α-fluoro-6β-nitroso derivative *(18)*[2]. The latter on standing reverted to the monomer, and tautomerized to the 5α-fluoro-6-oxime *(19)*, which was deaminated with nitrous acid to give the 5α-



Scheme 1. Synthesis of 17α-ethynyl-6,6-difluoro-19-nortestosterone *(13)* and derivatives from 19-nortestosterone *(1)*.



Scheme 2. Details of the reaction of nitrosyl fluoride with 3β,17β-diacetoxy-5(6)-estrene *(2)*.

fluoro-6-one *(3)*. *(3)* could also be obtained from the nitroimine *(17)* by treatment with neutral alumina (activity III). Mild treatment of the fluoroketone *(3)* with SF_4 and HF in CH_2Cl_2 gave 3β,17β-diacetoxy-5α,6,6-trifluoroestrane *(4)* in high yield which was then converted to the key intermediate 6,6-difluoro-4-estrene-3,17-dione *(7)* by mild acid hydrolysis, oxidation with CrO_3 in acetone followed by dehydrofluorination with alumina. Reduction of *(7)* afforded the diol *(8)*, which was selectively oxidized with dichlorodicyanobenzoquinone (DDQ) to give 6,6-difluoro-19-nortestosterone *(9)*. Conversion of *(9)* to the ketal *(10)* with ethylene glycol and oxalic acid catalyst in benzene followed by oxidation with CrO_3 in pyridine gave the 17-ketone *(11)* which was ethynylated using sodium acetylide in dimethyl sulfoxide solution. Treatment of the ethynylated ketal *(12)* with 90% acetic acid at room temperature yielded 17α-ethynyl-6,6-difluoro-19-nortestosterone *(13)*. *(7)* can also be converted directly into *(11)*.

The 6,6-difluoro modification enhanced both the oral progestational and oral anti-uterotrophic activity of 17α-ethynyl-19-nortestosterone[3].

Lecture at Darmstadt on September 23, 1970 [VB 261 IE]
German version: Angew. Chem. *83*, 116 (1971)

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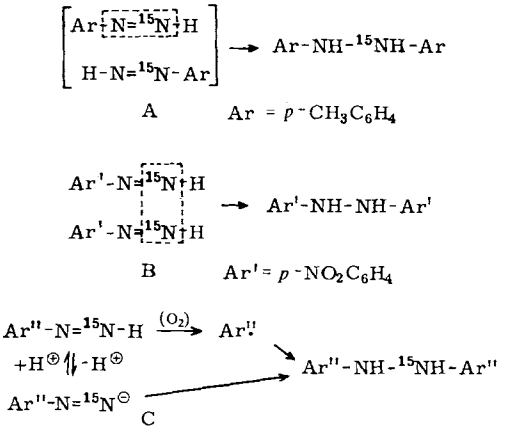
[1] *G. A. Boswell, Jr.*, J. Org. Chem. *31*, 991 (1966).
[2] *G. A. Boswell, Jr.*, Org. Chem. *33*, 3699 (1968).
[3] *W. H. Rooks II* and *R. I. Dorfman*, Contraception *1*, 403 (1970).

Rearrangements of Nitrogen Compounds Having Electronegative Substituents

By *Albert Heesing*[*]

Base-catalyzed rearrangement of guanidines bearing electronegative substituents leads, in the presence of quinones, to quinone semicarbazones. The action of acids or bases on quinone semicarbazones – and generally on derivatives of aryldiazenecarboxylic acids – leads essentially to the corresponding phenol (or to the aromatic hydrocarbon). Hydrazobenzene derivatives are also formed: *via* the aryldiimine intermediates. A variety of mechanisms have been proposed (see *e.g.* Ref. [1]) for this condensation, during which nitrogen is eliminated.

In our studies of the formation of hydrazobenzenes from deuterium- and ^{15}N-labeled compounds we have found three different reaction routes:



1) Two molecules of *p*-tolyldiimine react in acid solution *via* a concerted mechanism (A), eliminating N_2 without N–N bond cleavage, to give the hydrazo derivative.

2) In an acid medium, *p*-nitrophenyldiimine decomposes, with cleavage of the N–N bond, the β-nitrogen being liberated as N_2 (B).

3) In alkaline solution the N–N group remains intact in all cases. This reaction proceeds stepwise (C): aryldiimine and aryl radical react to give the final product.

On the basis of these findings it could be shown that:

a) In the Meerwein reduction of diazonium salts the aryl radicals[2] are not formed *via* the aryldiimine oxidation stage since no hydrazo compound is formed. While aryl radicals could be trapped in crossover experiments no aryldiimine could be intercepted.

b) Likewise, reduction of diazonium salts with H_3PO_2 does not involve aryldiimines. The aryl radicals detected in this reaction[3] could not be intercepted in crossover experiments (with *p*-tolyldiimine; reaction type A), thus affording additional proof of the concerted nature of reaction A in acid solution.

Lecture at Krefeld-Uerdingen on December 10, 1970 [VB 264 IE]
German version: Angew. Chem. *83*, 116 (1971)

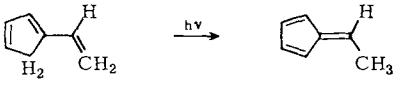
[*] Prof. Dr. A. Heesing
Organisch-Chemisches Institut der Universität
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[1] *E. M. Kosower, P. C. Huang,* and *T. Tsuji*, J. Amer. Chem. Soc. *91*, 2325 (1969).
[2] *R. Werner* and *C. Rüchardt*, Tetrahedron Lett. *1969*, 2407.
[3] *D. U. Banthorpe* and *E. D. Hughes*, J. Chem. Soc. *1962*, 3314.

A photooxidation of alkanes by nitrobenzene takes place (under nitrogen) on irradiation with a high-pressure mercury arc lamp according to a report by *J. W. Weller* and *G. A. Hamilton.* Alcohols and carbonyl compounds are formed in good yields, *e. g.* cyclohexanol and cyclohexanone in 50% yield (w.r.t. O content of used nitrobenzene) from cyclohexane. Investigation of the photooxidation of 2-methylbutane showed that the relative reactivity of primary, secondary, and tertiary hydrogens using a pyrex filter is 1:19:300; using a vycor filter this ratio is 1:7:110. The photooxidation of either pure *cis*- or pure *trans*-1,2-dimethylcyclohexane leads to the same ratio (1.6:1) of *cis*- and *trans*-tertiary alcohols. The reaction involves initial hydrogen atom abstraction from the alkane and subsequent reactions of the alkyl radical with nitrobenzene. / Chem. Commun. *1970,* 1390 / –Ma.

[Rd 275 IE]

A photochemical sigmatropic 1,7-shift of hydrogen in a semicyclic triene, 1-vinylcyclopenta-1,3-diene *(1),* has been observed for the first time by *L. J. M. van de Ven, J. L. M. Keulemans-Lebbink, J. W. de Haan,* and *H. Kloosterziel.* UV irradiation of *(1)* in 2,2,4-trimethylpentane or ether at −5° C

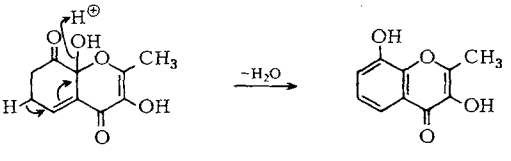


(1) *(2)*

(high-pressure mercury arc lamp) affords 6-methylfulvene *(2)* almost quantitatively. The shift presumably proceeds suprafacially. 1,7-Sigmatropic shifts have hitherto been observed only in cycloheptatriene and its derivatives. / Chem. Commun. *1970,* 1509 / –Ma.

[Rd 277 IE]

The formation of aromatic compounds from D-glucuronic acid and D-xylose under weakly acid conditions has been investigated by *T. Popoff* and *O. Theander.* The following compunds have been identified alongside the known reaction products furan-2-aldehyde, reductic acid, and furan-α-carboxylic acid after treatment of D-glucuronic acid in aqueous solution (pH = 3.5–4.5, 96°C, 48 h): pyrocatechol, 2,3-dihydroxytoluene, 2,3-

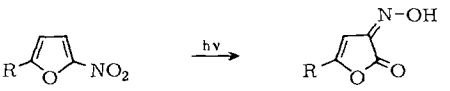


(1) *(2)*

dihydroxybenzoic acid, 2,3-dihydroxyacetophenone, 3,8-dihydroxy-2-methylchromone *(2)* and its precursor *(1).* The latter three compounds are also formed from D-xylose. The complex formation reaction involves fragmentation and recombination of carbohydrate fragments. / Chem. Commun. *1970,* 1576 / –Ma.

[Rd 278 IE]

The photorearrangements of 2-nitrofuran and 2-nitropyrrole have been investigated by *R. Hunt* and *S. T. Reid.* Irradiation of 2-nitrofuran in methanol or acetone with a medium-pressure mercury arc lamp gives 3-hydroxyimino-2-oxo-2,3-Dihydrofuran *(1),* m. p. 132°C. 5-Methyl-2-nitrofuran affords the methyl derivative. 2-Nitropyrrole analogously yields 3-hydroxyimino-2-oxo-2,3-dihydropyrrole, m. p. 210°C (dec.). The photoreaction presumably involves initial rearrangement to nitrite followed by thermal or photochemical cleavage to a furyl-



(1)

oxyl radical and NO and subsequent radical recombination at C-3. Correspondingly, 2-nitrofuran behaves like conjugated nitroalkenes (rearrangement of β-methyl-β-nitrostyrene to 1-phenyl-1-hydroxyiminopropan-2-one). / Chem. Commun. *1970,* 1576 / –Ma.

[Rd 279 IE]

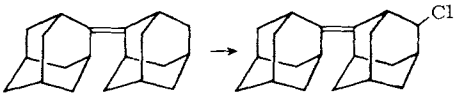
The structure of the aluminate ion in alkaline solutions has been investigated by *R. J. Moolenaar, J. C. Evans,* and *L. D. McKeever.* They measured IR, Raman, ^{23}Na and ^{27}Al NMR spectra at concentrations of 0.5 to 6 mole/l in H_2O and D_2O solutions. The spectra at low Al concentrations are consistent with the predominant existence of tetrahedral $Al(OH)_4^-$. At concentrations above 1.5 mole/l the vibrational spectra show new bands and the ^{27}Al resonance is broadened. These phenomena are interpreted as being due to condensation of $Al(OH)_4^-$ to $Al_2O(OH)_6^{2-}$. No evidence for AlO_2 occurring in the solutions was found. / J. Phys. Chem. *74,* 3629 (1970) / Hz.

[Rd 280 IE]

Molecular motions in crystalline *o*- and *m*-carboranes have been studied by *R. H. Baughman* using NMR, X-ray diffraction, and calorimetric techniques. Both molecules are nearly regularly icosahedral. At 25°C the ^1H resonance line second moment is 0.71 G^2 for *o*-carborane and 0.82 G^2 for *m*-carborane; a rigid lattice would require theoretically 34 G^2, rapid isotropic reorientation 0.63 G^2. The *o*-isomer was also studied at lower and higher temperatures: at about +4° C a phase transition with a transition enthalpy of 0.84 kcal mol^{-1} and an entropy of 3.0 e. u. was detected. Below this transition, molecular reorientation still proceeds relatively fast. Down to −130° C no further phase transition was found, indicating that either an order-disorder transition lies below −130° C, or the entropy is different from zero at 0°K. At about +200° C translational motions of molecules in the lattice effect a further decrease in NMR line width. / J. chem. Physics *53,* 3781 (1970) / –Hz.

[Rd 281 IE]

The anomalous chlorination of adamantylideneadamantane *(1)* is the subject of a report by *J. H. Wieringa, J. Strating,* and *H. Wynberg.* Compound *(1),* a reactive though strongly sterically hindered olefin, reacts *e.g.* with bromine to give the bromonium bromide. Reaction with chlorine at room temperature, on the other hand, yields only a polychlorinated product. At

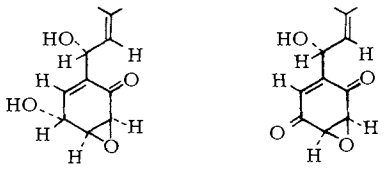


(1) *(2)*

−20° C a powder could be isolated, which, on the basis of its insolubility in non-polar solvents, could be a chloronium chloride. On warming it loses chlorine and HCl; the crystals remaining behind consist of starting material *(1),* 4e-chloroadamantylideneadamantane *(2),* and a little disubstituted material. Tetrahedron Lett. *1970,* 4579 / –Ee.

[Rd 282 IE]

The structures of panepoxydone and some related metabolites produced by the fungi *Panus rudis* and *P. conchatus (Basidiomycetes, Agaricaleae)* have been elucidated by *Z. Kis, R. Closse, H. P. Sigg, L. Hruban,* and *G. Snatzke:* panepoxydone *(1),* panepoxydione *(2),* neopanepoxydone, isopanepoxydone, 7-

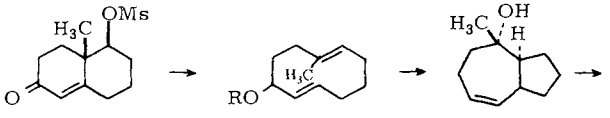


(1) (2)

deoxypanepoxydol, neopanepoxydol. The absolute configurations were deduced from CD measurements and by comparison with structurally related compounds such as epoxydone, terreic acid, and terremutin. Compounds (*1*) and (*2*) inhibit the propagation of the mast cell tumor P-815 in mice. / Helv. Chim. Acta *53*, 1577 (1970) / –Ma.

[Rd 283 IE]

A new synthesis of hydroazulenes by stereochemically selective transannular cyclization of cyclodecadienyl derivatives has been reported by *J. A. Marshall* and *W. F. Hufman*. Reaction of the unsaturated keto mesylate (*1*) with diborane in THF and subsequent treatment with $NaOCH_3$ in methanol affords the cyclodecadienol *(2)* in 60% yield. Solvolysis of the *p*-nitrobenzoate *(3)* in dioxane/water leads to hydroazulenol *(4)* (70%), which



(*1*) (*2*), R = O (*4*)

(*3*), R = p-$NO_2C_6H_4CO$

on hydrogenation yields the alcohol *(5)*. *(5)* can also be obtained from *trans*-hydroazulene. / J. Amer. Chem. Soc. *92*, 6358 (1970) / –Ma.

[Rd 284 IE]

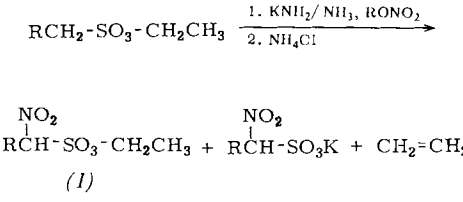
Novel light-sensitive protecting groups have been reported by *A. Patchornik, B. Amit,* and *R. B. Woodward*. Irradiation of amino acid derivatives, whose amino function is blocked by the 6-nitroveratryloxycarbonyl or 2-nitrobenzyloxycarbonyl group, with light of wavelength > 3200 Å (concentration: 10^{-2} – 10^{-3} mole/l; duration: 1–24 h; solvent: dioxane, $CHCl_3$, THF, dimethoxyethane, alcohols, ethanol/water, or ether/water) leads to quantitative cleavage of the groups without influencing even light-sensitive amino acids such as tryptophan. The yield of amino compound, however, is not quantitative since an intermediary aldehyde probably reacts with the amino compound. The amino compound (amino acid, peptide) is quantitatively liberated only on addition of aldehyde reagent during the photoreaction. 2,2'-Dinitrobiphenylylmethoxycarbonyl amino acid derivatives exhibit the best deblocking effect. The COOH function blocked by 2,2'-dinitrobiphenylylmethanol is liberated quantitatively on irradiation without addition of other compounds. / J. Amer. Chem. Soc. *92*, 6333 (1970) / –Ma.

[Rd 285 IE]

Ozonization of a secondary amine has been studied by *P. S. Bailey, J. E. Keller,* and *T. P. Carter jr.* 2-Methyl-2-nitropropane, *tert*-butylammonium chloride, and derivatives of the *tert*-butyl group liberated on formation of the nitro compound were identified as major products of ozonization of di-*tert*-butylamine. In contrast to the ozonization of *tert*-butylamine no ozonate anion radical was formed. A primary product of ozonization is di-*tert*-butyl nitroxide which is apparently formed, together with di-*tert*-butylammonium ion, by reaction of initially produced amine-ozone adduct with a second molecule of amine. Formation of all other products can be explained by ozonization of the nitroxide. / 159th Meeting Amer. Chem. Soc. *1970*, ORGN 61 / –Ma.

[Rd 287 IE]

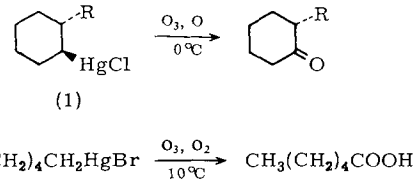
The synthesis of aliphatic α-nitro sulfonic esters *(1)*, a new class of compounds, has been described by *H. Feuer* and *M. Auerbach*. Aliphatic sulfonic esters react with KNH_2 and alkyl nitrates in liquid NH_3 to give (*1*). Reaction of the neopentyl ester yields (*1*) as sole product. Reaction of the ethyl ester with, *e.g.*, butanesulfonate affords not only ethyl 1-nitro-1-butanesulfonate but also the potassium salt of 1-nitro-1-butanesulfonic acid. The latter compound is formed by β-elimination in the ester part of the molecule during nitration. The



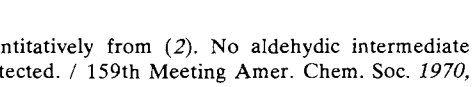
nitration was also used successsfully for the production of tertiary α-nitro sulfonic esters. / 159th Meeting Amer. Chem. Soc. *1970*, ORGN 101 / –Ma.

[Rd 288 IE]

Ozonolysis of organic mercurials has been studied by *P. E. Pike, P. G. Marsh,* and *W. L. Waters*. Primary and secondary alkylmercury compounds were ozonized in CH_2Cl_2 at about 0° C. Compounds (*1*), R = OCH_3 and (*1*), R = H, gave the corresponding ketones (about 60% isolated). *n*-Hexanoic acid was



(1)



formed quantitatively from (*2*). No aldehydic intermediate could be detected. / 159th Meeting Amer. Chem. Soc. *1970*, ORGN 62 / –Ma.

[Rd 289 IE]

Improved specific enzyme electrodes for urea and amino acids have been produced by *G. G. Guilbault* and *E. Hrabankova*. The urea electrode consists of urease in a polyacrylamide matrix that was covered with an ammonium ion electrode. The amount of NH_4^+ produced at the surface by the urea-urease reaction serves as a measure of the urea present in a sample of body fluid (in the range 0.01–10‰). The amino acid electrode contains amino acid oxidase immobilized in polyacrylamide gel. L- or D-amino acid specificity is ensured by use of the respective enzyme. / 159th Meeting Amer. Chem. Soc. *1970*, ANAL 86 / –Ma.

[Rd 286 IE]

The photoconductivity of liquid nitrobenzene has been investigated by *G. Brière* and *F. Gaspard*. Two types of experiments were carried out: firstly, the time dependence of the photocurrent generated by continuous illumination (436 nm) and low voltage pulses was measured. Secondly, with a continuous voltage applied across the cell, the current-time behavior was followed after switching on or off the light source. In both experiments the liquid was stirred. The first experiment showed that after a time of the order of 10^3 sec a saturation current is developed which is independent of voltage over a wide range: this means that the same amount of ions disappear per unit time as are generated photochemically. If a high enough voltage is chosen for the second experiment recombination can be neglected compared with elimination of ions by discharge at the electrodes. Combination of the results of both experiments yields values of $k_R = 2.6 \times 10^{-7} cm^3 sec^{-1}$ and $k_D = 5.8 \times 10^{-13} sec^{-1}$ respectively for the ion recombination and dissociation rate constants. For comparison, ion recombinations in aqueous solutions are faster by a factor of about 10^{10}. In addition to photodissociation and ion recombination, irreversible processes also take place in the system. / Chem. Phys. Letters *7*, 537 (1970) / –Hz. [Rd 291]

Rates of formation and decomposition of oxonium hydrates have been evaluated by *C. E. Young, D. Edelson,* and *W. E. Falconer.* The authors used an ion drift tube attached to a time-of-flight mass spectrometer. Argon-water mixtures with 0.5–1.8% water vapor partial pressure were investigated at total pressures of 0.6–3.0 torr at 337° K. Analysis of the flight times as functions of the drift tube pressure and accelerating potential can be used to evaluate the kinetics of the reactions

$$H_3O^+(H_2O)_{n-1} + H_2O + Ar \underset{k_{-n}}{\overset{k_n}{\rightleftharpoons}} H_3O^+(H_2O)_n + Ar$$

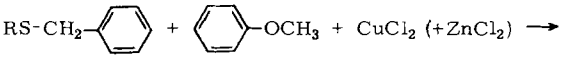
For n=1,2,3, the rate constants are $k_1=6\times10^{-28}$; $k_2=6\times10^{-28}$; $k_3=2\times10^{-28}$ cm^3sec^{-1}. The rate constants of the reverse reactions are of the order of 10^{-13} cm^3sec^{-1}. / J. Chem. Phys. *53,* 4295 (1970) / –Hz.

[Rd 290 IE]

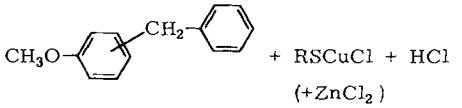
Ionization constants of water in mixtures with organic solvents are reported by *E. M. Woolley, D. G. Hurkot,* and *L. G. Hepler.* The difference between the EMF values of cells with glass and Ag/AgCl electrodes containing acid and alkaline solutions was evaluated. With the same solvent composition and at low ionic strengths which are approximately equal for the solutions compared, liquid junction potentials can be considered very nearly equal. p$K(H_2O)$ values are given for mixtures of water with ethanol, *n*-propanol, isopropanol, *tert*-butanol, ethylene glycol, acetone, and 1,4-dioxane containing up to 60 wt% of the organic component. Generally, pK values increase with increasing organic concentration, with the exception of glycol-water mixtures. The anomalous behavior of glycol can not, as yet, be explained. / J. Phys. Chem. *74,* 3908 (1970) / –Hz.

[Rd 292 IE]

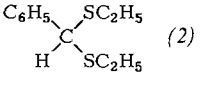
The benzylation of aromatic compounds with benzyl sulfides in the presence of $CuCl_2$ and $CuCl_2/ZnCl_2$ has been investigated by *T. Mukaiyama, K. Maekawa,* and *K. Narasaka.* Compounds of type *(1)* [*e.g.*: R=CH_3 (76% yield); 4,5-dihydro-2-thiazolyl (57%); 4-pyridyl (79%)] and *(2)* react with aromatic compounds such as anisole, *m*-xylene, toluene, or benzene in the presence of $CuCl_2/ZnCl_2$ (equimolar amounts) to give the corresponding benzyl derivatives. If the reaction is carried out in



(1)



(+$ZnCl_2$)



(2)

the presence of $CuCl_2$ alone the yields of benzylation product are low. $CuCl_2$ reacts with the sulfide to form a complex which is activated by $ZnCl_2$ but not by $AlCl_3$, $SnCl_4$, $FeCl_3$ or ether-BF_3. / Tetrahedron Lett. *1970,* 4669 / –Ma.

[Rd 293 IE]

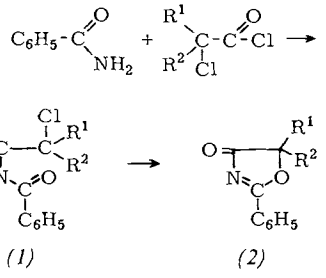
Methyl and *n*-alkylketones have been synthesized by *G. H. Posner* and *C. E. Whitten* from carboxylic acid chlorides and lithium diorganocopper reagents:

$$R'\text{-}COCl + R_2CuLi \rightarrow R'COR$$

The reagents are readily obtained by reaction of methyl-, ethyl-, or *n*-butyl-lithium with CuI (molar ratio 2:1) in ether at 0° C under N_2; the alkylations, which require 15 min were performed at −78° C with 3 mmoles Cu reagent per mole of acid chloride. Functional CO groups and halogen atoms of the acid chloride are not attacked under the extremely mild conditions. Yields are high; for example: *n*-$C_5H_{11}COCl$, R=CH_3, 81%; R=*n*-C_4H_9, 79% yield: cyclo-$C_6H_{11}COCl$, 86%, 80%; $(C_6H_5)_2CHCOCl$, 93%, 90%; *tert*-C_4H_9COCl, 84%, 90%; 3,5-$(CF_3)_2C_6H_3COCl$, 92%, 75–80%; *p*-$O_2NC_6H_4COCl$, 50%. / Tetrahedron Lett. *1970,* 4647 / –Ma.

[Rd 295 IE]

A novel synthesis of 4(5*H*)-oxazolones is reported by *Y. Shyamsunder Rao* and *R. Filler.* α-Chlorodiacylamines *(1),* which are prepared by heating equivalent amounts of benzamide and α-chlorocarboxylic acid chloride, afford the 4(5*H*)-oxazolones *(2)* in 50–70% yield when treated with NaH in dry benzene.



(1) *(2)*

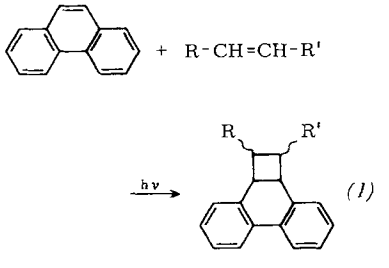
/ Chem. Commun. *1970,* 1622 / –Ma.

[Rd 296 IE]

Pentafluorobenzenesulfenyl chloride *(1)* is, according to a report by *P. Sartori* and *A. Golloch,* a suitable reagent for introduction of the pentafluorophenylthio group. The authors prepared *(1)* in yields greater than 90% *via* a new route, namely by chlorination of C_6F_5SH, $C_6F_5SSC_6F_5$, or $Hg(SC_6F_5)_2$ in CCl_4. *(1),* b.p. 48°C / 1 torr, is thermally very stable. When heated under vacuum in a flow system at temperatures between 700 and 750°C it is converted quantitatively into chloropentafluorobenzene and elemental sulfur. *(1)* can be oxidized to the sulfonyl chloride; it can be converted *e.g.* into the sulfenyl piperidide by reaction with piperidine and into the amide $C_6F_5S\text{-}NH\text{-}SC_6F_5$ by reaction with NH_3 in ether. Reaction with KCN leads to the thiocyanate C_6F_5SCN. / Chem. Ber. *103,* 3936 (1970) / –Ee.

[Rd 297 IE]

Photocycloaddition of olefins to phenanthrene have been observed by *T. Miyamoto, T. Mori,* and *Y. Odaira.* Irradiation of phenanthrene with a high pressure mercury arc lamp under nitrogen at room temperature in the presence of a) *cis*-dichloroethylene, b) *trans*-dichloroethylene, c) dimethyl maleate, d) acrylonitrile in ether or ethanol leads to tetrahydrocyclobuta-



(1)

phenanthrenes *(1).* Addition occurs at the 9,10 position. In examples a) and b) the *cis,trans,trans-*, *cis,cis,cis-*, and *cis,trans,cis*-adducts are obtained in 22, 7, 3 and 25, 32, 0.6% yields respectively while in c) the *cis* adduct is formed in 62% yield and in d) the *syn*- and *anti*-adducts in 78% and 20% yield respectively. / Chem. Commun. *1970,* 1598 / –Ma.

[Rd 294 IE]

Table of Ion Energies for Metastable Transitions in Mass Spectrometry. By *J. H. Beynon, R. M. Caprioli, A. W. Kundert* and *R. B. Spencer.* Elsevier Publishing Company, Amsterdam-London-New York 1970. 1st Edit., 506 pp., bound, Dfl. 70.00.

"Metastable ions", *i.e.* ions which decompose on the way from the ion source to the collector, play an important role in the investigation of mass-spectrometric decomposition processes because they yield information on cleaved-off particles. Metastable ions lead to the formation of relatively broad bands in the corresponding mass spectra. However, the low intensity of such bands makes them difficult or impossible to detect.

To facilitate the task of detecting metastable ions *Beynon*, one of the authors, has evolved an elegant method: normal ions from the ion source of a double-focusing apparatus pass through the field-free space with a kinetic energy E into the electrostatic sector field. In contrast, metastable ions, which are decomposed in the field-free space, carry only the fraction $F = Em_2/m_1$ of the kinetic energy of the parent ions, m_1 being the mass of the parent ions and m_2 that of the daughter ions. These ions can only pass through the retarding potential if the voltage V in the electrostatic sector field is reduced to the value Vm_2/m_1. If the voltage is continuously changed from 0 to V, one obtains a spectrum of the kinetic energies of all metastable transition processes. Since in this case there is no overlap with the normal spectrum, this technique constitutes a very sensitive method for investigating metastable ions.

With the aid of the present tables the corresponding metastable transition processes can easily be determined from the kinetic energy values, which can be read off directly. This book will therefore be an indispensable and time-saving tool for all laboratories in which IKE (ion kinetic energy) spectra are used for the study of metastable ions.

Spiteller [NB 923 IE]

Disinfection. Edited by *M. A. Bernarde.* Marcel Dekker, Inc. New York 1970. 1st Edit., xiii, 466 pp., $ 24.50.

This book demonstrates that disinfection still belongs to an underdeveloped area of research. In many cases ultraconservatism – "disinfection rituals" – stands in the way of the few new possibilities in the field of disinfection. In practice, disinfection is primarily a question of money and of suitable staff.

The book is aimed at all people working in research, hygiene, and the foodstuffs industry who are interested in new discoveries in the field of disinfection. Nineteen authors have contributed to the book, most of them giving detailed reports on specialized fields. The collaboration of the team of authors, however laudable in itself, sometimes leads to overlapping and unnecessary repetition.

One is inclined to divide the book into a theoretical and a practical and technical part. The first part would have been improved by condensing some parts and expanding others. Bacterial metabolism and mechanisms of action should perhaps have been put in one chapter and the sites of action of the common disinfectants and (in somewhat more detail) those of some antibiotics could have been included in the metabolism and biosynthesis schemes. A few basic theoretical aspects could also have been transferred from the practical and technical section into the theoretical section which is rounded off with chapters on disinfection kinetics, the destruction of resistant bacterial spores and viruses, the scope for the application of gas disinfection, and the disinfection problem *per se* (American hospitals).

Further reports on disinfection procedures in hospitals (Japan, USSR) form the transition to the practical and technical section. From this point on the book assumes something of the character of a practical manual (which the editor wanted to avoid). Disinfection in the milk industry is treated in too much detail; there is also a lot of information on the disinfection processes in the foodstuffs, fish, and drinks industries.

The layout of the book is attractive. Some points of confusion and a few printing errors should have been avoided.

Hans Bender [NB 920 IE]

Progress in Molecular and Subcellular Biology. Vol. 1. By *B. W. Agranoff, J. Davies, F. E. Hahn, M. G. Mandel, N. S. Scott, R. M. Smillie,* and *C. R. Woese,* edited by *F. E. Hahn.* Springer-Verlag, Berlin-Heidelberg-New York 1969. 1st Edit., vii, 237 pp. 32 figures, bound, DM 58.–.

Molecular biology has pleged itself, like a kind of religious society, to a "central dogma" according to which DNA alone regulates all life processes; it is always seeking new frontier regions in which to carry out its mission and establish regularities that can be explained by physical phenomena. The law that derives from the central dogma is that of the "information flow" (nothing is added to the clarity of this concept by the fact that it is used so loosely and its meanings are so obviously varied), controlled according to time, place, and quantity by membranes, hormones, and nerve cells. Thus, after molecular genetics and many other things, the study of nervous processes has now caught the interest of molecular biologists.

The series "Progress in Molecular and Subcellular Microbiology" begins in a very promising way. The editors have commissioned several skilled and knowledgeable authors to write within a wide, general framework. In a very well constructed section *C. R. Woese* deals with what intellectual and heuristic implications the solution of the genetic code had for molecular biology. *B. W. Agranoff* has contributed a stimulating chapter on the role of macromolecules in the cerebral function. He comes to the conclusion that the higher animals have a natural behavior repertoire which is "learnt" in a similar way to immune body formation. A typical chapter on subcellular biology is that which deals with the autonomic biosynthesis of chloroplasts, written in lucid detail by *R. M. Smillie* and *N. S. Scott.* An information molecule controls the formation of a complex structure: taking 5-fluorouracil as an example, *H. G. Mandel* describes what happens when artificial blockages and defects are incorporated into such information molecules, while *J. Davies* investigates the natural band width of the replication mechanisms.

All of these sections are informative and well presented, although many doubts remain as to the persuasive power of so many ephemeral arguments. However, it is only recently that exceptions to the central dogma and to the reliability of the translation mechanisms have become known. The present book is successful in its intention and will also serve to familiarize the chemist with the thinking and the problems of the molecular biologist.

L. Jaenicke [NB 924 IE]

Quantenmechanik und Theorie des Molekülbaues (Quantum Mechanics and the Theory of Molecular Structure) By *W. M. Tatewski.* Verlag Chemie GmbH, Weinheim/Bergstr. 1969. 1st Edit., 126 pp., numerous figures, stitched, DM 19.50.

The title of this book is misleading; it is not an introduction to current theory on chemical bonds and the electronic structure of molecules. The author has instead set out to show, on the basis of quantum mechanics, how well founded the concepts and laws of classical structure theory are and where they can be applied. He comes to the conclusion that at present it is not possible in the case of polyatomic molecules to derive either exactly or even approximately the concept of chemical bonding

or the structural formula from the general principles of quantum mechanics. The only generally valid theoretical criterion for the stability or instability of the states of a system of nuclei and electrons is the presence of a minimum in the corresponding energy surface.

The usual concepts of theoretical chemistry, for example valence electrons, electron pair bonding, σ-π-separation, and localization or delocalization of electrons, naturally have no place in such a strict quantum theory of molecular structure. This argument is presented in a very convincing manner, but it will be of little help to the chemist in his attempts to understand the relationships between the structure and properties of molecules.

Martin Klessinger [NB 930IE]

Lehrbuch der anorganischen Chemie (Textbook of Inorganic Chemistry). By *A. F. Hollemann* and *E. Wiberg*. Walter de Gruyter & Co., Berlin 1971. 71st – 80th Edits., xxxii, 1209 pp., bound, DM 58.–.

Holleman's textbook of inorganic chemistry, which in the fourth decade of this century, having seen 21 editions, had been on its last legs, was given an entirely new form by *Egon Wiberg* in 1942. Teachers and students alike received the new work with enthusiasm. It pointed the way for teaching in inorganic chemistry and in less than 30 years appeared in another 50 editions.

Hitherto (21st–70th editions[1]) the scope and content of the work have been oriented primarily toward chemistry students preparing for their preliminary examinations in inorganic chemistry. It also provided adequate information for those working in other fields of chemistry and preparing for their diploma and doctorate examinations. In the present editions (71st–80th) a wish long cherished by *Wiberg* has at last been fulfilled. The textbook has been revised and, above all, expanded in such a way that it can now also be used profitably by advanced inorganic chemists. Thus, the text has been extended to cover 1209 pages instead of the previous 766, the index of names has been increased by a further 600 entries, and 6300 new keywords appear in the subject index. Introductory and comparative surveys, figures, tables, molecular and lattice structures, three-dimensional diagrams, short biographies, etymological derivations, and many other things besides have been considerably extended. An extremely valuable feature is the inclusion of 450 references to collective reviews and monographs: this gives interested readers easier access to sources without further increasing the size of the textbook. The concentration on problems of inorganic chemistry has unfortunately meant that many technological processes have fallen the victim of abridgement. These were a strong point of the earlier editions. The author used a total of 25,000 personal index cards. It is difficult to believe that one person could be capable nowadays of preparing such a comprehensive work covering the whole field of inorganic chemistry.

It would be impossible for such a book to be without any faults. The critic should bear in mind, however, that this work is written for inorganic specialists. A person who looks at inorganic chemistry *e.g.* from the point of view of an expert in bond theory, molecular dynamics, or structural clarification will find little to satisfy him. It is difficult to suit everyone. In the ultimate analyses every critic should write a textbook for his own private use.

Time will tell whether it was wise to expand the textbook so much in one volume. I myself think that it would have been better to have two 700-page volumes, an introductory one and an advanced one. Young people who carry pleasure as their banner and not work, who leave school incapable of independent academic work, who cling to the apron strings of their tutors and instructors, and who have to have their knowledge predigested for them will not be able to manage this book if their teachers do not break down the factual content into much smaller units and build up the students' knowledge step by step. Although the price of the book is fairly reasonable, some features are to be deplored. The covers of the two copies sent to the reviewer were already torn when they were unpacked, one of the pairs of red-green spectacles was faulty, and many bond lines were incorrectly printed (pp. 396, 397, 409, 414, *etc.*). The pop colors of the cover (orange on sky blue) are regrettable. It is also surprising that the publishers should publish 10 editions at once instead of taking into account the suggestions for corrections received from readers after one or two editions. As it is, errors will be perpetuated over many years.

It should also be pointed out that the index of names could cause confusion as to the scientific significance of the entries, although the frequency of the citations is governed mainly by the output (monographs) of the authors quoted, and that the chronological table on the history of inorganic and general chemistry is made up, doubtless to the regret of all inorganic chemists that have been working on research in the past few decades, almost exclusively of discoveries in the field of physics (preservation of parity, the first reactor built in West Germany, the discovery of the antineutrino and of the Ω particle, construction of the ruby laser, *etc.*).

The reader might be inclined to take these criticisms as an indication that the reviewer is concerned much more with the faults of the book than with its good points. This could not be further from the truth. If I were asked whether I could name a better textbook on inorganic chemistry my unhesitating answer would be no.

Ulrich Wannagat [NB 932IE]

[1] Cf. Angew. Chem. internat. Edit. *4*, 265 (1965).

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50 Years of Hydrogen Bond Theory[**]

By Maurice L. Huggins[*]

The "hydrogen bond" or "hydrogen bridge" concept has proved to be one of the most useful structural concepts in modern science. The properties of substances containing hydrogen bonds depend on the strength, symmetry, and polarity of these bonds. These characteristics, in turn, are related to the effective electronegativities of the bridgehead atoms, the distance between these atoms, and the degree of coupling with other hydrogen bonds. Symmetrical hydrogen bonds exist in the FHF^- and $H_5O_2^+$ ions and in some acidic compounds. Coupled hydrogen bond systems exist, for example, in ice, liquid water, hydroquinone clathrates, starch, cellulose, polypeptides, nucleic acids, KH_2PO_4, and silicate hydrates. It is suggested that systems of coupled, nearly symmetrical, hydrogen bonds should be interesting subjects of further research.

1. Introduction

It is my prejudiced belief that, except for electron-pair bonding between atoms and Coulombic attractions and repulsions between ions, the most important structural principle in chemistry and biology is that of hydrogen bonding. Hydrogen bonding is also of great importance in physics, crystallography, mineralogy, geology, meteorology, and various other "-ologies". I therefore take pride in the fact that I was the first to introduce the hydrogen bond concept: the idea that a hydrogen atom can be bonded at the same time to two other atoms[1–6]. That was just 50 years ago.

It seemed reasonable to me that a nonbonding electron pair – a "lone pair", as I called it – should have a considerable attraction for a positively charged proton, even if that proton is already bonded to another atom.

2. Early Applications

This idea was first used to explain tautomerism in acetoacetic acid esters and similar compounds, the interaction of ammonia with water, the structure of sulfuric acid, and similar phenomena. Soon thereafter, *Latimer* and *Rodebush*[6] used the concept very effectively in discussing the behavior of polar compounds in water solution.

I first found definite evidence for the existence of hydrogen bonds in the crystal structure of ammonium

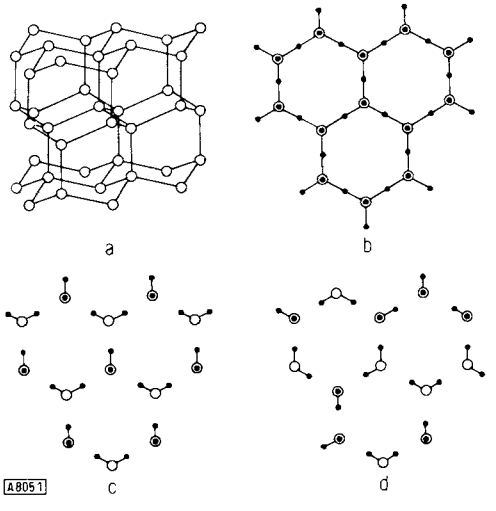


Fig. 1. The structure of ice: a) Arrangement of oxygen atoms. b) Distribution of hydrogen and oxygen atoms in a section of the structure, assuming (incorrectly) that the hydrogen bonds are symmetrical. c, d) Two of the many ways of distributing the hydrogen atoms with unsymmetrical hydrogen bonds.

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Woodside, Calif. 94062 (USA)

[**] Adapted from a lecture delivered before the Royal Swedish Academy of Sciences at Stockholm on October 8, 1969, and at six other institutions.

chloride[4]. In this compound the hydrogen atoms must be located on the centerlines between nitrogen and chlorine atoms. I predicted that ice would be found to have a structure in which each oxygen is surrounded tetrahedrally by four other oxygen atoms, with the hydrogens presumably on the centerlines between oxygen atoms. Before long, *W. H. Bragg*[7] showed that the structure is actually like this (Fig. 1a).

Since then, studies by X-ray diffraction, neutron diffraction, infrared spectroscopy, and other techniques have confirmed the existence and importance of hydrogen bonds in thousands of compounds.

3. Symmetrical and Unsymmetrical Hydrogen Bonds

At first I considered a hydrogen bond between two like atoms to be symmetrical (see Fig. 1b). Later[8], chiefly because of the relatively small shifts of infrared band frequencies when a compound containing hydroxyl groups goes from the gaseous state to the liquid or solid state, I concluded that they are usually unsymmetrical (Fig. 1c and 1d). Now that the hydrogen positions can be precisely located by X-ray and neutron diffraction studies, we know that this is the case.

The conclusion that the hydrogen bonds are unsymmetrical in such substances as water was independently arrived at by *Bernal* and *Fowler*[9] at about the same time. In a number of instances, however, the hydrogen bonds between like bridgehead atoms are definitely symmetrical, with the hydrogen atom in the middle of the bridge in each case. The first such bridge to be identified was that in the FHF^-ion[10]. Some others will be discussed presently.

4. Potential Energy Curves

With the aim of achieving a better understanding of the properties of hydrogen bonds, I calculated[11] potential energy curves for the hypothetical motion of a hydrogen atom along the centerline between two bridgehead oxygens. As an approximation, I assumed that the energy of interaction between the hydrogen and each oxygen depends on the interatomic distance in the same way as in the OH molecule. (Errors in this assumption would not affect the qualitative conclusions drawn from comparisons of the different curves.) The graphs obtained (Fig. 2, left) show how the shape of the potential energy curve changes as the oxygen-to-oxygen distance changes. For the distances usually observed there are two minima, indicating an unsymmetrical hydrogen bond. For somewhat shorter oxygen-to-oxygen distances only a single minimum is found, meaning that the hydrogen bridge is symmetrical. In agreement with this result, all known symmetrical bridges have very short O · · · O distances.

The effect of altering the effective negative charges on the bridgehead oxygens was examined by adding a Coulombic term to the previously calculated energies. This of course modifies the shapes of the curves symmetrically, if the change is made for both oxygens, and unsymmetrically, if made for only one (see Fig. 2, right).

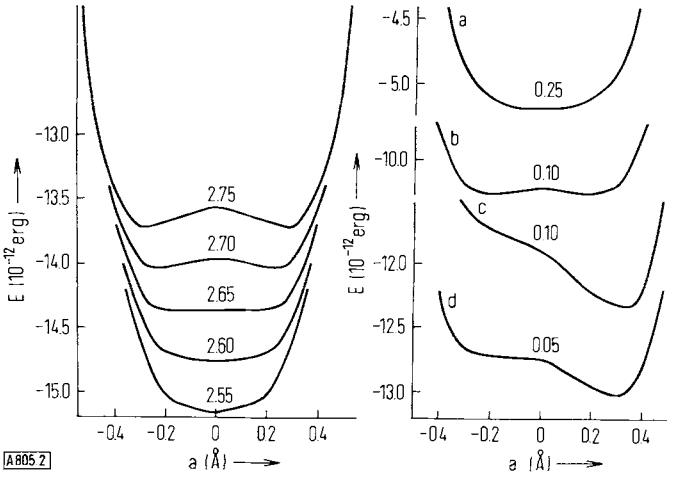
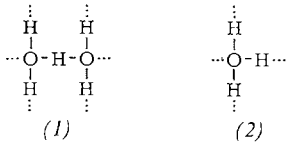


Fig. 2. Theoretical potential energy curves for OHO hydrogen bonds, showing (left) the dependence on the distance between the bridgehead oxygens (numbers on curves, in Å) and the effect of adding a Coulombic attraction term α (right, curves a and b) to both O-H interactions and (right, curves c and d) to only one O-H interaction (α is given by the numbers on the curves).

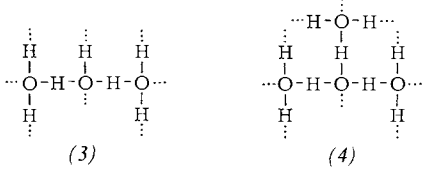
5. Hydrogen and Hydroxide Ions

Consideration of the model curves in Fig. 2 suggested[11] that hydrogen ion in water solution might consist essentially of a proton at the center of a short, strong, symmetrical hydrogen bond joining two H_2O groups together, as shown in *(1)*, instead of the H_3O^+ unit *(2)* usually assumed[*].



(1) *(2)*

There is no *a priori* reason for eliminating the possibility of $H_7O_3^+$ *(3)* or $H_9O_4^+$ *(4)* or larger ions, but the stabilization of the short, single minimum, hydrogen bonds by the excess positive charge should become less as the average excess charge per oxygen atom decreases.



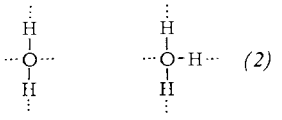
(3) *(4)*

The composition and structure of the cation in acidic aqueous solutions are not yet known. In some crystals of known structure H_3O^+ moieties have been found. In others, $H_5O_2^+$ units, with short, symmetrical hydrogen bonds, exist[12–14]. These units have also been found in acidic solutions in dimethyl sulfoxide[15].

The formation of symmetrical hydrogen bonds in $H_5O_2^+$ ions can be rationalized in the following way: Comparing

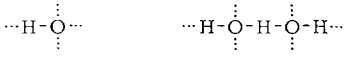
[*] The positive charge has been omitted from all formulas of this kind.

the oxygens in a water molecule and a hypothetical H_3O^+ ion *(2)*, the latter would have a smaller effective negative charge. It would attract the close protons less and so the hydrogen bonds formed by these close protons would be more nearly symmetrical. If one of these protons forms a symmetrical hydrogen bond, however, that increases slightly the effective negative charge on the oxygen under consideration, perhaps enough to prevent the other two close hydrogens from also forming symmetrical hydrogen bonds.



(2)

Comparing similarly the oxygens in a water molecule and a hypothetical OH^- ion *(5)*, the latter would have a larger effective negative charge. It would thus have a greater attraction for each of the more distant bridging hydrogen atoms and tend to make them more nearly symmetrical. If this tendency is great enough, one or more symmetrical hydrogen bonds may be formed, giving a structure that can be represented by the formula *(6)* or a more complicated structure.



(5) *(6)*

In this discussion the effect of the changes in effective negative charges on the oxygen-to-oxygen distance has been neglected. For the hydrogen ion this effect would decrease this distance and so favor the formation of a symmetrical hydrogen bond. For the hydroxyl ion the oxygen-to-oxygen distance would be increased and a symmetrical hydrogen bond made less likely. The actual situation must be determined by future experiments.

The mechanism of conduction, by either hydrogen ion or hydroxyl ion, presumably involves a Grotthuss chain process[11,16], with protons passing over an energy hump from one side of an unsymmetrical hydrogen bond to the other or with unsymmetrical hydrogen bridges changing to symmetrical ones, and *vice versa*.

6. Effective Charges

Since the potential energy curves showed the importance of the effective negative charges on the bridgehead atoms, I attempted to estimate these charges, as functions of the kinds and numbers of atoms to which the bridgehead atoms are attached[17]. Recently, in connection with a study of hydrogen bonding in certain silicate hydrates[18], I have made similar estimates for the types of bridgehead oxygens in these crystals.

These rough estimates, for the effective bridgehead atom charges exclusive of the contribution of the hydrogen atom of the bridge being considered, are calculated as follows: To a charge of -2 for the "oxide ion", I add $+1$ for a silicon neighbor, $+1/6$ for a sodium neighbor, $+3/4$ for a close hydrogen of a hydrogen bridge, and $+1/4$ for a distant hydrogen of a hydrogen bridge. The charges so calculated are listed in Table 1.

Table 1. Estimated effective charges on bridgehead oxygen atoms in certain hydrated silicates.

Structon formula [a]	Calculated charge
O(H··,··H,··Na)	− 0.83
O(H··,2··H)	− 0.75
O(Si,2··Na)	− 0.67
O(Si,··H,··Na)	− 0.58
O(Si,2··H)	− 0.50
O(Si,2··H,··Na)	− 0.33
O(2H··,··Na)	− 0.33
O(Si,3··H)	− 0.25
O(2H··,··H)	− 0.25
O(Si,H··,··Na)	− 0.08
O(Si,H··,··H)	0.00

[a] The hydrogen of the bridge for which the calculation is made is not included in the expression in parentheses.

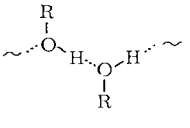
For the first five types listed in Table 1, the hydrogens of the bridges being considered are at the close ends of the bridges, near the oxygens for which the charge calculation is made. The total calculated charge, including the contribution of the bridging hydrogen, is thus 0.75 units more positive than the value listed, in each case. For the last 6 types, the bridging hydrogen is at the far end of the bridge in each case; hence the total calculated charge is 0.25 units more positive than that given. As would be expected, the calculated total charges are never very far from zero. (Table 1 of Reference[18] gives the calculated total charges for the oxygens in $Na_2(H_2SiO_4) \cdot nH_2O$ and $Ca_3(HSiO_4)_2 \cdot 2H_2O$ crystals.)

Until more quantitative methods become available, estimates of effective charges on the bridgehead atoms should be useful in comparing dissymmetries and energies of different hydrogen bonds.

It may be noted, incidentally, that some of the oxygens in these silicate hydrates, in addition to being bonded to a silicon atom, are at the weak ends of *four* hydrogen bonds. Since an oxygen atom has only four electron pairs in its valence shell, this shows that, as previously assumed, the hydrogen-to-oxygen attractions at the weak end of an unsymmetrical OHO hydrogen bridge are largely Coulombic.

7. Coupled Hydrogen Bonds

Crystals of organic hydroxyl-containing compounds invariably contain chains or rings of hydrogen bonds, with each oxygen atom a bridgehead for two H-bonds:



(7)

(See Fig. 3 to 5).

In cellulose, one hydroxyl group of each ring probably makes a hydrogen bond to the oxygen atom in the next

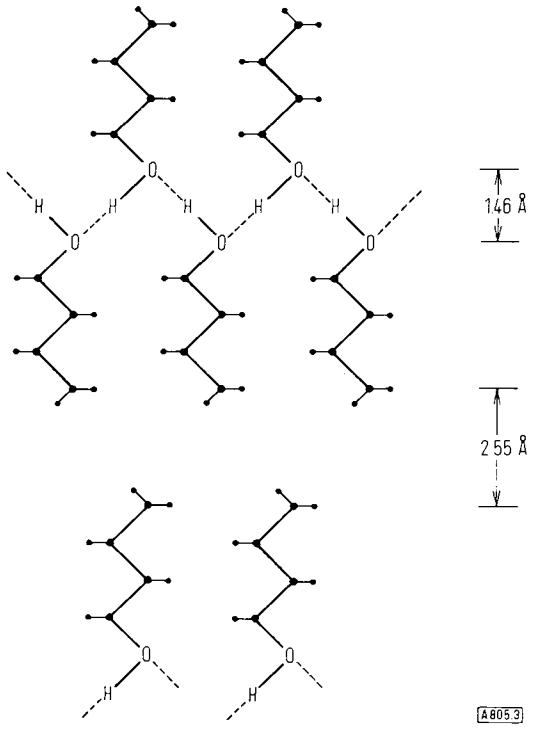


Fig. 3. Diagrammatic representation of the structure of a crystalline alcohol [17].

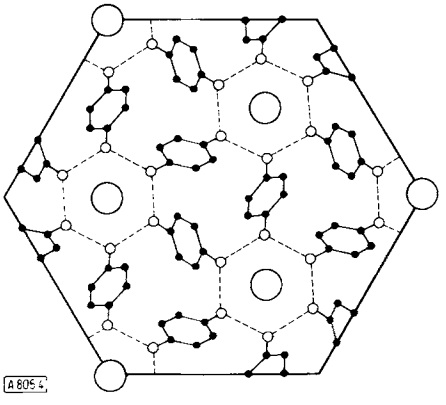


Fig. 4. Projection of the structure of a hydroquinone clathrate [19]. Hydrogen bonds are represented by dashed lines. The large circles indicate sites for guest molecules.

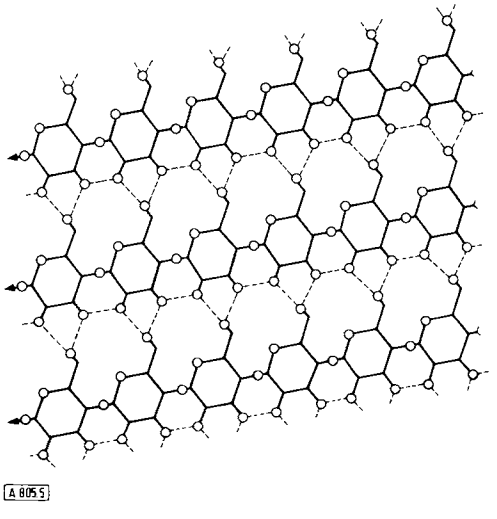


Fig. 5. Proposed spiral structure for a form of amylose starch [20–22]. Dashed lines denote hydrogen bonds. (Imagine that the pattern has been drawn on a paper cylinder and that this cylinder has been slit parallel to its axis and then flattened.)

ring. The other hydroxyl groups, I believe, form chains of hydrogen bonds, stitching adjacent molecules together in approximately the same way as successive turns of the helix are stitched together in the postulated model for amylose starch[22,23].

Crystals of carboxylic acids also contain chains or rings of hydrogen bonds, connected together through the carboxyl groups (Fig. 6).

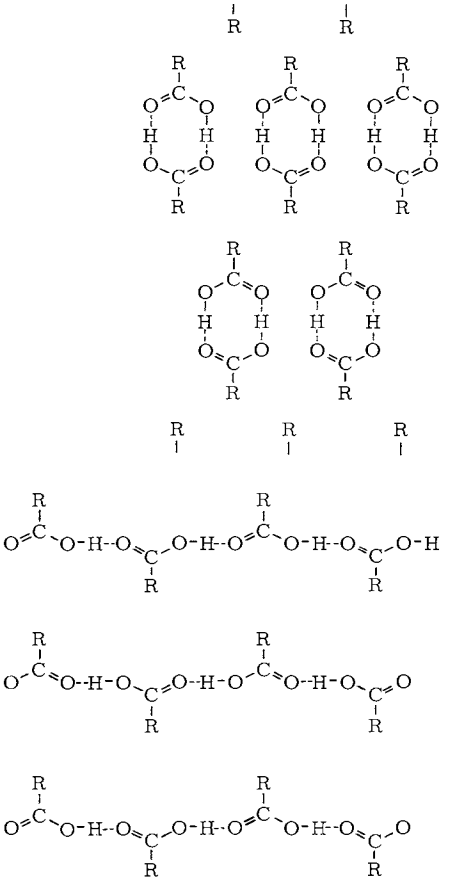


Fig. 6. Diagrammatic representations of two types of structures in crystalline fatty acids [17].

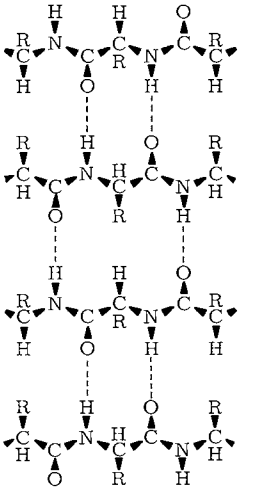


Fig. 7. NHO hydrogen bonding between chains in fibrous proteins and polypeptides [17, 23–25].

A similar situation exists in proteins, polypeptides, and other compounds containing CO-NH groups (see Fig. 7 and 8).

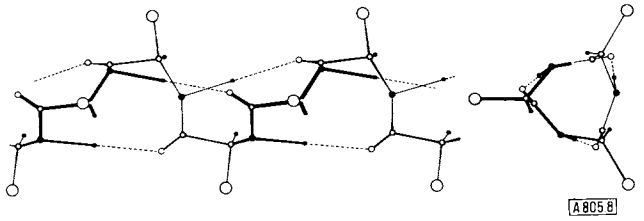


Fig. 8. Two projections of one of a series of helical structures with NHO hydrogen bonds, proposed for proteins and other polypeptides [25–27].

With reference to protein and polypeptide structures, it may be noted that the concepts of NHO hydrogen bonding, parallel and antiparallel extended chain structures, helical structures, and the planar peptide unit were introduced by me (contrary to many statements in the literature) over 30 years ago[17,23–25,27]. At that time it was impossible for me to determine which of a number of helical structures actually exist in proteins. That decision could only be made after X-ray diffraction data on synthetic polypeptides became available.

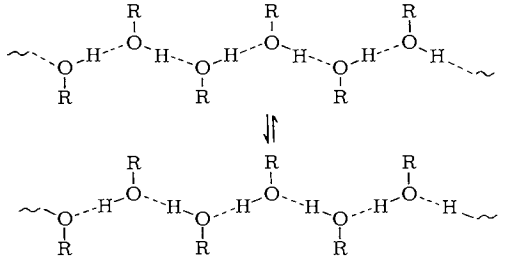
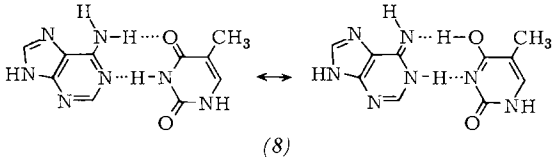


Fig. 9. Reversal of polarization in a chain of coupled unsymmetrical hydrogen bonds.

In a chain or ring of hydrogen bonds connecting hydroxyl groups, as depicted (for a chain) in Figure 9, one would expect some electron resonance between the two oppositely polarized structures shown. This resonance would be small for very unsymmetrical hydrogen bonds, but should become large and important in systems of H-bonds that are symmetrical or nearly so. This resonance increases the stability of the system and makes each hydrogen bridge more nearly symmetrical than it would be without the resonance. Similar resonance should occur in the carboxylic acid and amide chains and rings, since the hydrogen bonds are connected together through conjugated bond systems. The two "extreme states" differ by interchange of the lines and dots in the hydrogen bond formulas and by interchange of the single and double bond lines in the O=C–O and O=C–N formulas.

Another kind of resonance[28], which I believe to be equally important, can be described as the synchronized oscillation of the hydrogens of the hydrogen bridges in the chain or ring and the electron clouds in the oxygen atoms or OCO or OCN groups between the hydrogen bridges. This should be more important the broader and less steep the potential energy curve near its minimum, hence more important the closer that curve approaches the single minimum type (*i.e.*, the more symmetrical the hydrogen bond when the bridgehead atoms are alike). This synchronized oscillation resonance, like electron resonance, tends to make each hydrogen bond more nearly symmetrical (or closer to the single potential energy minimum type) than it would otherwise be.

The hydrogen bonding within the "base pairs" in nucleic acids is often referred to, but the important stabilization of these bonds by electron resonance and synchronized oscillation resonance is rarely mentioned. With regard to the electron resonance, two of the contributing extreme states are those indicated in formula *(8)* for the bonding between adenine and thymine.



(8)

Other zwitterion states doubtless also contribute importantly, as do (in my opinion) the synchronized oscillations of the atoms, especially the hydrogens, and electron clouds around the ring.

Coupling between hydrogen bonds can also exist if they are suitably connected in a two- or three-dimensional net structure. This situation exists, for example, in crystals of KH_2PO_4 and some other ferroelectric materials[22] (Fig. 10).

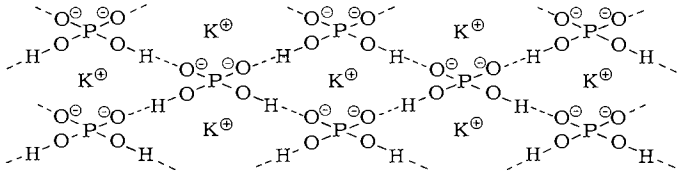


Fig. 10. Diagrammatic representation of the structure in a domain of a KH_2PO_4 crystal [22]. Note the polarization, which can be reversed by shifting of each hydrogen from one side of its hydrogen bond to the other side.

Within a domain, the polarization of all the hydrogen bonds, and likewise that of all the intervening phosphate groups, is presumably uniform. By changing the external electric field, this polarization can be reversed, indicating (as could also be inferred from the short oxygen-to-oxygen distance for the hydrogen bonds) that the hydrogen bonds are nearly symmetrical, with a very small potential energy hump between the two minima.

A similar reversal of polarity, by external means or by chemical alteration of the chain ends, should be possible for chains of coupled hydrogen bonds, if the energy barriers are small enough. I suggest that it should be possible, with the aid of the principles that I have outlined, to design and synthesize many substances with strongly coupled hydrogen bridges and very low energy barriers, even at room temperature. It should prove interesting to study the properties of such systems, as dependent on structural factors, the kinds of atoms or groups con-

necting the hydrogen bridges together, the kinds of other atoms or groups attached to the bridgehead oxygens or nitrogens, the presence of proton donors or acceptors or electron donors or acceptors, *etc.*, at the ends of the chains or the surfaces of the domains, and the external electric field. In some cases it should be possible to transmit pulses or waves across the system or to set up standing wave patterns. I predict that the synthesis and study of such systems will prove very exciting, perhaps leading to models for the transmission of nerve impulses[29] or for brain activity, including memory retention.

8. Conclusion

In concentrating, in this article, on the aspects of the subject in which I have myself been most interested, I have not intended to belittle the great contributions to the development and application of hydrogen bond theory made by thousands of others. Much fine work has been done and yet much more obviously remains to be done.

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The Synthesis of Physiologically Active Peptides[**]

By Rolf Geiger[*]

In addition to the classical protective groups and linkage methods for the synthesis of peptides, there are now a number of new techniques that allow the synthesis of fairly long peptide chains without racemization. In the present progress report, the diagnostic and therapeutic importance of the analogs obtainable by chemical synthesis is illustrated by some examples, particularly from the field of the peptide hormones secreted by the neurohypophysis, oxytocin and vasopressin, as well as corticotropins and releasing hormones. With the advance of synthesis technique, it will become possible to include fairly complicated molecules, such as insulin and even enzymes in such considerations.

1. Introduction

We know of no physiological process that takes place without the participation of proteins. For example, all enzymes belong to this class of substances, and enzymes are the catalysts for the synthesis, transformation, and degradation of organic material in nature.

From the chemical standpoint, proteins are peptides, *i.e.* compounds in which amino acids are joined to one another by amide linkages to form molecules that are often extremely large[1].

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The distinction between peptides and proteins is historical, and has now become problematic. The limit chosen was the size of molecule up to which these compounds pass through a natural dialysis membrane. This corresponds to a molecular weight of about 10000. According to this definition, peptides consist of up to approximately 100 amino acid residues, whereas proteins or macropeptides contain more than about 100 amino acid residues.

The chemist seeks to bring proteins within the scope of the more general term "peptides". The biologist, on the other hand, looks on a protein rather as a molecule that, unlike the smaller peptides, can have a certain autonomous reactivity as well as characteristic physical properties. This reactivity is seen *e.g.* physically in the ability of fibrous proteins to contract, or chemically in the catalysis of specific reactions by enzymes.

The properties of the proteins are encoded in the sequence of the amino acids in the peptide chain, *i. e.* the primary structure. The genetic information for the amino acid sequence is contained in the base sequence of the deoxyribonucleic acids (DNA) in the gene.

The activation of a gene section triggers off the biosynthesis of the corresponding protein. It begins with the transcription of the information into a ribonucleic acid (RNA), which acts as a messenger and ultimately effects the translation of the information into the amino acid sequence at the site of protein synthesis.

This is where extreme difficulties arise for the chemist who is concerned with the analysis of proteins or peptides, and who is trying to obtain these molecules by synthesis. Though the growth of the number of proteins whose amino acid sequences have been established is becoming steadily faster, it is only a short time since the first venture was made into the synthesis of a protein, this protein being the enzyme ribonuclease.

Over the past 15 years, the true domain of the synthetic worker has been peptides up to a chain length of about 40 amino acids. Many hormones having high physiological activities and fascinating properties were discovered in this field.

In the organism such substances are synthesized in a matter of seconds. A team of experienced chemists, on the other hand, takes weeks, months, or even years for such a synthesis. It thus seems uneconomical at first sight to try to compete with nature in this field. This unfavorable light changes, however, when one considers that the completion of a gene mutation involving the replacement of a single amino acid within a protein takes *e. g.* 7 to 10 million years in the case of hemoglobin[2], whereas once a scheme has been developed, the chemist can apply it to the synthesis of many similar peptides within a short time.

The synthesis of peptides thus allows the study of structure-action relationships. Such investigations are possible only within very narrow limits by chemical or enzymatic modification of naturally occurring peptides.

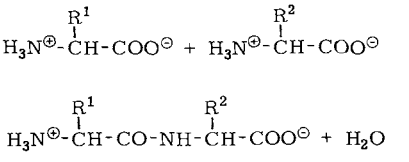
A further incentive to synthesis may lie in the difficulty of obtaining many peptides having comparatively simple structures. These often occur only in small concentrations even at the site of their formation, *e. g.* in a gland or in the serum. It is only by synthesis that they can be made available in sufficiently large quantities for biological research or for medicinal use.

Finally, even in this class of substances, a clear synthesis provides proof of a proposed structure.

Parallel with the synthesis of a growing number of peptides, the arsenal of methods and technical experience has also grown during the past 20 years.

2. Protective Groups and New Condensation Methods

It is well known that peptides formally result from the condensation of amino acids with elimination of water. Scheme 1 shows the principle of this reaction for the synthesis of a dipeptide.



Scheme 1

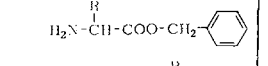
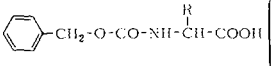
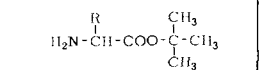
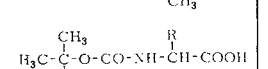
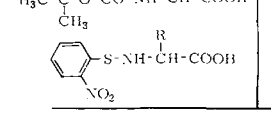
If the reaction is to yield a single product, there must be only one free amino group and one free carboxyl group; in other words, the functional groups that are not to react must be blocked by protective groups. The situation is complicated by the fact that side chains R may also contain reactive groups, and these must then also be blocked.

We thus need two types of protective groups, *i. e.* one type that intermittently protects the α-amino and carboxyl groups and liberates them again selectively, and another type that blocks the other functional groups throughout the synthesis. All these protective groups must be capable of being removed at the end of the synthesis under conditions that do not affect the sensitive final product.

Though many protective groups have been recommended, only a few have found general and extensive use. Since most peptides are reasonably stable in acidic media, combinations of protective groups having graded acid labilities are preferred nowadays.

Three important types are shown in Table 1. These are the benzyl type, the *tert*-butyl type, and the phenylsulfenyl type[1]. Benzyl ester groups protecting carboxyl groups can be removed by

Table 1. Protective groups for amino acids during peptide synthesis.

Amino acid + protecting group	Name	Symbol	Removal
	Benzyloxy (benzyl ester)	OBzl	HBr, HF, hot trifluoroacetic acid, catalytic hydrogenation
	Benzyloxycarbonyl	Z	
	*tert*-Butoxy (*tert*-butyl ester)	OBu^t	*e.g.* cold trifluoroacetic acid
	*tert*-Butyloxycarbonyl	Boc	
	2-Nitrophenylsulfenyl	Nps	*e.g.* weak acid + indole

catalytic hydrogenation. It was discovered only later that protonic solvolysis of benzyl esters can also be accomplished with acids such as hydrogen iodide or hydrogen bromide in glacial acetic acid, as well as hydrogen fluoride or hot trifluoroacetic acid.

To protect the amino group, the benzyl residue cannot be attached directly to the nitrogen since the C-N bond is too stable. So that the benzyl residue will again be attached by an ester linkage, a urethane is prepared. After the removal of the benzyl residue, the carbonic acid escapes as CO_2, and the amino group is again in the free state.

The *tert*-butyl residue is used in a similar manner to protect amino and carboxyl groups. *tert*-Butyl esters are resistant to alline hydrolysis and to catalytic hydrogenation, but are rapidly attacked by acids even under conditions such that benzyl residues are still stable, *e.g.* by cold trifluoroacetic acid.

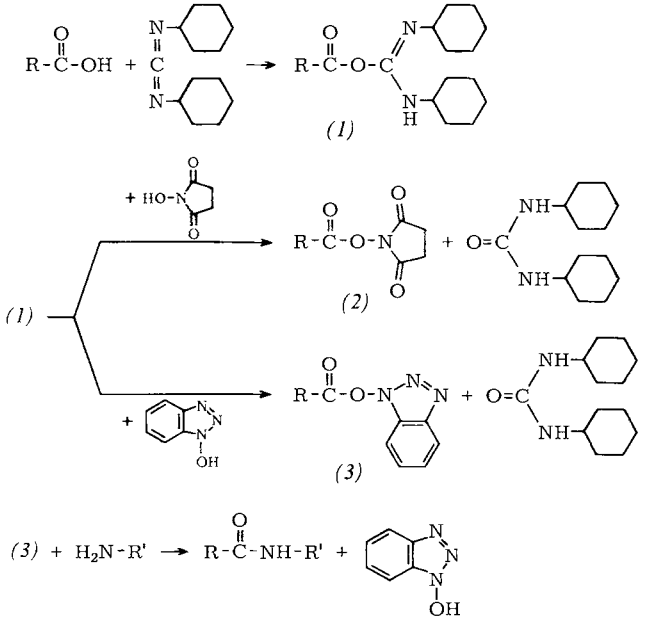
A further increase in acid sensitivity is achieved with the nitrophenylsulfenyl residue. However, this can only be used for the protection of the amino group. The S-N bond can be broken merely by a nucleophilic attack in dilute acid but, because this reaction leads only to an equilibrium, and since the nitrophenylsulfenyl group is readily transferred to the indole ring of tryptophan, an "interceptor", *e.g.* indole, is also added to take up the sulfenyl residue and to bind it irreversibly[3].

More or less practicable solutions, mostly based on the benzyl and *tert*-butyl types mentioned above, have also been discovered for the masking of hydroxyl, mercapto, and guanidino groups, which can also occur as constituents of amino acids[1].

Another central problem of peptide chemistry is the condensation of amino acids or peptide fragments without racemization.

The formation of a peptide linkage between an amino group and a carboxyl group with elimination of water requires energy. This energy is supplied through the chemical activation of the carboxyl group. In this high-energy state, the optically active amino acids readily undergo racemization. This usually results in loss of biological activity. The most pressing requirement for any condensation method is therefore the prevention of racemization.

Only one of the "old" techniques fully satisfied this requirement; this was the azide method, which was developed by *Curtius*[1]. It ultimately also became possible to reduce racemization to a minimum in the carbodiimide method[1], which has been known for a long time (Scheme 2).



Scheme 2

Dicyclohexylcarbodiimide (DCC) first adds on to the carboxylic acid to give an isourea derivative, which is extremely reactive and hence liable to suffer racemization. This compound is very rapidly attacked by certain *N*-hydroxy compounds that are added to the reaction mixture. This leads *e.g.* to the activated carboxylic acid derivatives *(2)* and *(3)*[4,5]. In the final step, *i.e.* the slow formation of the peptide linkage by aminolysis of *(2)* or *(3)*, the amine now reacts with this activated derivative, which is resistant to racemization despite its high reactivity, instead of with the readily racemized primary addition product.

It has recently been shown that the synthesis of peptides *via* mixed anhydrides with half-esters of carbonic acid[1] can also proceed without racemization under certain conditions[6].

A more recent variant of the synthesis technique still remains to be mentioned. This is *Merrifield*'s solid state synthesis[7] in which the amino acid is reversibly attached by the carboxyl end to a synthetic resin. The further steps in the synthesis now take place on this insoluble support, which is suspended in and swells in the solvent. After each reaction, excess reagents are simply washed out by solvent. Since the steps involved in the successive incorporation of the amino acids are repetitive, the synthesis can be automated. Though the results obtained so far by this interesting method have fallen short of expectations in many cases, it now allows the preparation of peptides containing up to about 12 amino acid residues with a considerable saving of time if satisfactory facilities are available for the purification of the initial crude peptide mixture and if knowledge and experience of the application of purity criteria are available.

We shall now discuss considerations that guide the synthesis of physiologically active peptides with the aid of a few selected examples.

3. The Hormones of the Neurohypophysis

Hormones have no autonomous reactivity such as is possessed *e. g.* by enzymes; they are messengers that trigger off a reaction or reaction chain only after being bonded to specific receptors at the site of action. Thus if we make changes in the amino acid sequence of a peptide hormone in order to study structure-action relationships, we are simultaneously exploring the receptor, though this method cannot provide particularly accurate information about its nature and topography.

The two hormones of the neurohypophysis, *i. e.* the labor-inducing oxytocin *(6)* and the antidiuretic and pressor substance vasopressin [Arg^8 vasopressin *(8)* and Lys^8 vasopressin *(9)*], for example, are recognized by the receptor only in their steric structure as determined by the cyclic form. Simple cleavage of the ring formed by a disulfide bridge or even a small increase in the ring size leads to disappearance of the homone action. A whole series of modifications are nevertheless possible.

Out of more than 150 known natural and synthetic peptides having analogous structures[1], a few are listed in Table 2. We recognize arginine vasotocin *(7)* which is assumed to be the parent hormone of this family. It is found in cold-blooded animals and in the pineal gland of higher vertebrates[8]. Starting from this compound, it is possible to imagine the differentiation into the oxytocin and the vasopressin series by stepwise gene mutation after gene reduplication[9].

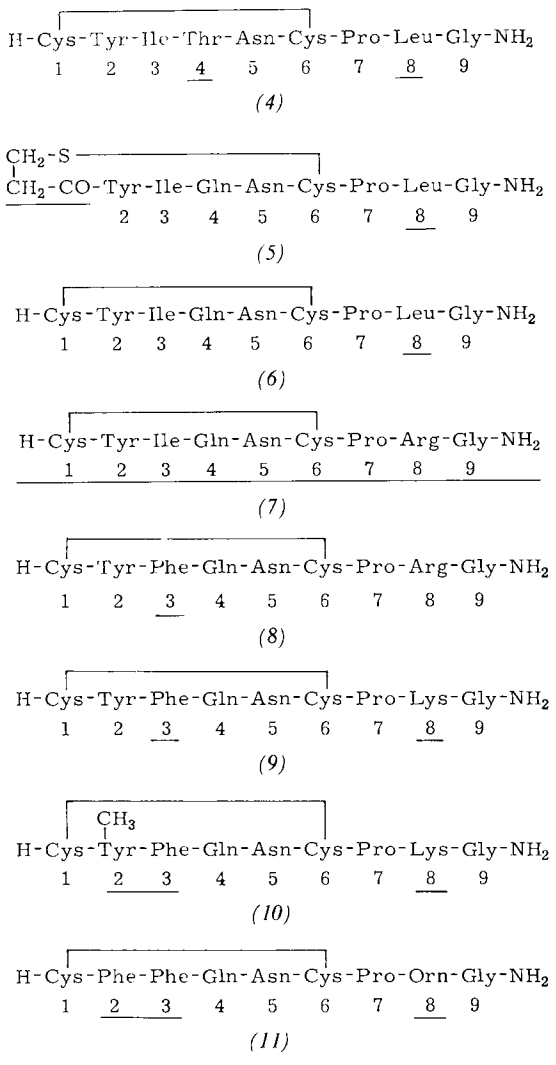


Table 2. Biological activities of the hormones of the neurohypophysis and its analogs (in I.U./mg).

Hormone or analog	Oxytocin effect (rat uterus)	Vasopressin effect: blood pressure (rat)	Vasopressin effect: antidiuretic action (rat)	Ratio blood pressure: antidiuretic action
Ile[4] Oxytocin *(4)* (synthetic)	900	0.4	3	1 : 7.5
Deaminooxytocin *(5)* (synthetic)	900	1	15	1 : 15
Oxytocin *(6)* (natural)	450	5	5	1 : 1
Arg[8] Vasotocin *(7)* (natural)	155	245	250	≈ 1 : 1
Arg[8] Vasopressin *(8)* (natural)	16	400	400	1 : 1
Lys[8] Vasopressin *(9)* (natural)	5	270	250	≈ 1 : 1
Methyl Tyr[2] Lys[8] vasopressin *(10)* (synthetic)	0.02	2.4	275	1 : 115
Phe[2] Orn[8] Vasopressin *(11)* (synthetic)	1	120	0.5	240 : 1

Alongside these natural hormones, synthetic peptides are now taking their place. Elimination of the amino group on the cysteine leads in the oxytocin series to deaminooxytocin *(5)*, which has a stronger biological action than the natural product.

To explain this phenomenon we must consider the biological breakdown of the peptides. Peptides are formed and broken down again in the body within a short time. It is therefore probably no accident that the body uses this very class of compounds for the sensitive, fast-acting, and also rapidly discontinuing "fine adjustment" of physiological processes, a very rapidly adjustable equilibrium being achieved by increasing or decreasing the supply.

Aminopeptidases break down the peptides from the amino end, and carboxypeptidases break them down from the carboxyl end. The rupture of certain bonds within the molecule, which is important in proteins, becomes less important in lower peptides.

Deaminooxytocin *(5)* is no longer susceptible to attack by the specific aminopeptidase for the breakdown of oxytocin. The molecule thus has a longer lifetime than the natural hormone. This is seen experimentally as an increased activity, provided that, as in the present case, the change in the structure does not appreciably reduce the bonding by the receptor.

The highly active threonine[4] oxytocin *(4)*, the synthesis of which was recently described by *Manning*[10], provided something of a surprise. Whereas more than 80 oxytocin analogs have been synthesized over the past 15 years, the only one that showed biological activity was deaminooxytocin, and the increase in that case was indirect, as it resulted from the longer lifetime of the molecule. In threonine[4] oxytocin, on the other hand, it appears that the bonding to the receptor and thus the as yet unknown primary effect of the hormone on the receptor is strengthened. In this respect, the natural hormone has now been dethroned by a synthetic "mutant".

The vasopressins are characterized above all by two physiological effects. They promote the reabsorption of water in the distal section of the renal tubules, *i. e.* they have an antidiuretic action. They also strengthen the contraction of the arterioles and capillaries, and so increase the blood pressure.

The vasopressins thus have several receptors. In view of the close structural relationship between the hormones, it is not surprising that the vasopressins also have a certain affinity for oxytocin receptors. Conversely, oxytocin also has a certain vasopressin action.

Variations within the peptide chain influence the vasopressin effects to varying degrees. This is particularly noticeable when the tyrosine in position 2 is slightly changed. Methylation of the phenolic OH group of tyrosine, as in *(10)*, leads practically to disappearance of the pressor action, whereas the antidiuretic action is slightly increased. Replacement of the tyrosine by phenylalanine, *i.e.* elimination of the OH group, on the other hand, leads to almost total disappearance of the antidiuretic action, while the pressor effect is less strongly influenced. This tendency is intensified by additional variation in position 8, as in *(11)*. Whereas the pressor action and the antidiuretic action, expressed in international units per mg, are balanced by definition in vasopressin, slight modification of the molecule is sufficient to increase the specificity of action by several orders of magnitude (see the last column in Table 2). A vasopressin with specific pressor activity is finding practical use in gynecology, where it should replace epinephrine as an additive in local anesthetics.

Shifts of the action spectrum have also been observed in the case of oxytocin, which induces milk ejection as well as contraction of the uterus; however, the changes in specificity observed here so far are not so pronounced.

4. Adrenocorticotropic Hormone[1]

Whereas only those changes that left the size of the molecule unchanged lead to highly active analogs in the case of the hormones of the neurohypophysis, an additional possibility is offered by shortening of the chain in the case of adrenocorticotropic hormone (ACTH, corticotropin).

The hormone consists of a chain of 39 amino acids (Scheme 3). It is formed in the adenohypophysis, *i.e.* the anterior lobe of the pituitary gland, and when bound by a receptor on the adrenal cortex it induces the secretion of the corticosteroids.

sequence 6–10 is common to both peptides, this small fragment must be essential for the initiation of the ACTH effect.

It is interesting to note that the same sequence is also responsible for the action of the melanophore-stimulating hormone (MSH)[1] and of the lipotropic hormone (LPH)[12]. It is only the sequences attached on either side of this fundamental unit that determine the receptors to which the active section will be bound, and so decide whether its action will be mainly corticotropic, melanophore-stimulating, or lipolytic.

The binding sequences also contribute to the biological activities. Even peptides consisting of 13–15 amino acids are almost as active as natural corticotropin, provided that the amino and carboxyl ends are protected against enzymatic breakdown (Table 3)[11].

However, the biological activity increases suddenly at a chain length of 17 amino acids to reach a value of about

```
H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-
  1   2   3   4   5   6   7   8   9  10  11  12  13  14

Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asp-Ala-Gly-Glu-Asp-
 15  16  17  18  19  20  21  22  23  24  25  26  27  28  29

Gln-Ser-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe-OH
 30  31  32  33  34  35  36  37  38  39
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(12)

```
ß-Ala-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-R
   1   2   3   4   5   6   7   8   9  10

                    X-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-R
                      6   7   8   9  10  11  12  13  14  15  16
```

X = CH_3-CH_2-O-CO
R = NH-$(CH_2)_4$-NH_2

Scheme 3. Human corticotropin *(12)* (top) and principle for the determination of the shortest biologically active sequence (bottom) on synthetic ACTH analogs (activity: 0.4 and 7 I.U./mg respectively).

Only a part of the molecule can be responsible for the hormone action, since even peptides containing about 20–24 amino acid residues, counted from the amino end, retain the full biological activity. Further shortening of the peptide chain results in a fast, but not yet abrupt, decrease in the ACTH activity. This alone suggests that the actual active region could be much smaller, and is enclosed by sequences that effect the bonding of this active region to the receptor.

To test this hypothesis, two peptides having severely shortened ACTH sequences were compared (Scheme 3)[11]. The boxed region common to the two peptides is assumed to be the active sequence. The other parts of the molecule would then be responsible for bonding the sequence to the specific ACTH receptor. The terminal residues were so chosen that they protect the molecule against enzymatic degradation from the amino and carboxyl ends.

As the experiment showed, both peptides have a small but clearly measurable ACTH activity. Since only the 800 I.U./mg, which is approximately four times the activity of the natural hormone. Similar observations have been made on a peptide containing 18 amino acids, in which the amino end was blocked by D-serine and the carboxyl end by an amino group[13].

Table 3. Constitution and ACTH activity of synthetic ACTH analogs. The sequence 5–16 of the four analogs corresponds to that in the natural hormone [cf. *(12)*].

Compound [a]	No. of amino acids	ACTH activity [b]
ß-Ala-Tyr-Ser-Met-Glu-····-Lys-Lys-R 1 2 3 4 5 16 17	17	807 (533-1360)
ß-Ala-Tyr-Ser-Met-Glu-····-Lys-R 1 2 3 4 5 16	16	136 (86-202)
X-Ser-Met-Glu-····-Lys-Lys-R 3 4 5 16 17	15	149 (82-250)
X'-Glu-····-Lys-Lys-R 5 16 17	13	92 (70-120)

[a] R = NH–$(CH_2)_4$–NH_2; X = *p*–HOC_6H_4–CH_2–CH_2–CO; X' = H_3C–$(CH_2)_3$–O–CO.

[b] Values in I.U./mg; determination in rats after blockage with Dexamethasone®; 3rd Internat. Standard. $P = 0.95$.

The significance of these short-chain, biologically highly active corticotropins lies in their ability to penetrate mucous membranes more readily than the natural hormone because of their comparatively low molecular weight. Unlike the natural hormones, therefore, they can be applied sublingually or intranasally. Their increased duration of action, which extends over a few hours with suitable doses, tends toward an ideal ACTH therapy, which takes the diurnal rhythm into account. The time-action relationship of these new synthetic corticotropins corresponds to the rapid increase in the ACTH blood level in the morning and the slow return to the normal low value.

5. Insulin and Ribonuclease

Chemical synthesis no longer presented any fundamental difficulties in connection with the hormones discussed so far, and it was possible to concentrate entirely on the study of structure-action relationships. Insulin, on the other hand, which is one of the most extensively discussed peptide hormones from the medicinal point of view, still presents many problems not only to the physiologist but also to the chemist. Chemically speaking, insulin is an embodiment of a new type. It consists of two peptide chains linked to each other by two disulfide bridges. Another disulfide bridge exists within the A chain (Scheme 4).

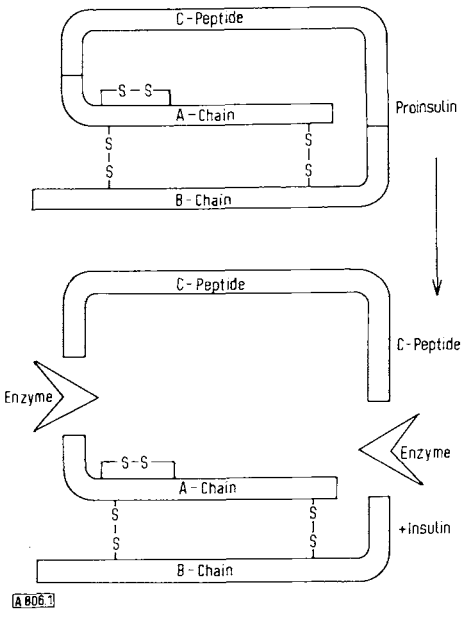
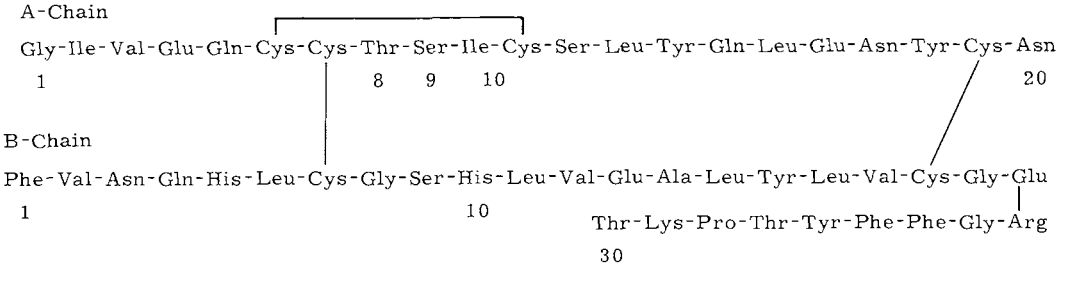


Fig. 1 Formation of insulin from proinsulin.

In the case of ribonuclease, which is an enzyme consisting of a peptide chain of 124 amino acids and containing four disulfide bridges (Fig. 2), reductive cleavage followed by reformation of the four disulfide bridges leads, not to the 105 possible monomolecular isomers, but to



Scheme 4. Human insulin. Bovine insulin contains Ala-Ser-Val in positions 8–10 of the A chain, and in both bovine and pig insulin, the B chain ends with Ala instead of Thr.

It has long been a puzzle how the body synthesizes such a molecule. *Steiner* discovered proinsulin[14], a single-chain precursor in which we again find the two chains of insulin. In this case they are joined by an intervening link, the connecting peptide or C peptide. When this C peptide has fulfilled its function of bringing the two parts of the chain into the appropriate position for the formation of the disulfide bridges, it is split off enzymatically and undergoes degradation (Fig. 1).

Though the chemical synthesis of insulin has already been accomplished[15], we are still far from finding a satisfactory solution to the problems associated with it. The synthesis of the two peptide chains presents greater difficulties than the synthesis of other peptides of comparable chain length. However, the limiting step is the specific combination of the two chains to form insulin. a quantitative yield of a single isomer, *i. e.* the fully active enzyme. The two insulin chains, on the other hand, lack the inherent directing force of ribonuclease. A mixture of many isomeric and polymeric compounds is therefore obtained.

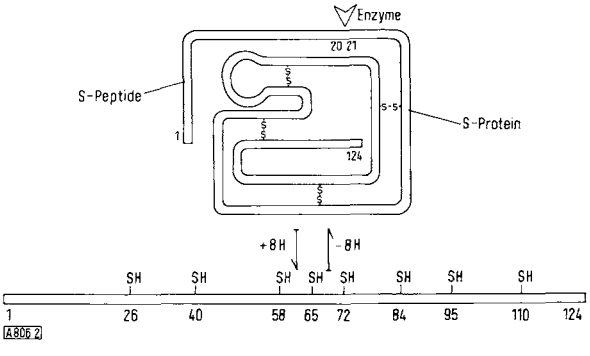


Fig. 2 Top: Oxidized (enzymatically active) and bottom: reduced ribonuclease.

Proinsulin, the one-chain precursor of insulin, behaves more like ribonuclease. About 70% recombination in accordance with the formula is obtained at high dilutions, though the yields under preparative conditions, *i.e.* at higher concentrations, are lower.

The parallels between ribonuclease and insulin or proinsulin can be followed still further. Ribonuclease is specifically cleaved by the enzyme subtilisin at a single point, *i.e.* between amino acids 20 and 21[16]. The enzymatic action of ribonuclease is retained, despite the breakage of the peptide chain at this point, and disappears only if the two fragments, the S peptide and the S protein, are separated from each other. If the two fragments are then reunited in solution, the strong intermolecular forces between the two peptides cause them to recombine immediately in the correct conformation to give the structure having the full enzymatic activity (Fig. 2).

The knowledge gained with ribonuclease was also applied to proinsulin. Attempts were made to reoxidize reduced proinsulin that had already been ruptured enzymatically at one or both cleavage points. However, the recombination yield was no higher than in the combination of A and B chains, *i.e.* these fragments of proinsulin also lack the directing forces that are inherent in the two fragments of ribonuclease.

However, reservations are necessary regarding the information obtainable from this experiment. The enzymatic cleavage of proinsulin is not confined to the elimination of the C peptide. There are two basic amino acids at each of the linkage sites, which are also entirely or partly eliminated in this reaction. The product that is finally isolated as the C peptide is not the actual fragment, but the intermediate link with four basic amino acids less.

There is thus a possibility that it is these basic amino acids that are responsible for the full development of the attractive forces between the three sections.

Since this question could not be answered using natural C peptide, it was necessary, in a synthesis consisting of about 120 steps, to synthesize a C peptide that had these four basic amino acids at the two ends[17]. Since the addition of this synthetic fragment had no effect on the yield in the recombination of A and B chains[18], we can expect no further help with the synthesis of insulin from this line of enquiry.

Moreover, synthesis *via* proinsulin is not very attractive from the economic point of view. In addition to the effort of synthesizing a peptide having more than 80 amino acids instead of two chains of 21 and 30 amino acids respectively, the method suffers from the unsatisfactory formation of the disulfide bridges. The elimination of the C peptide by an enzyme that we have not yet isolated and the loss of this sequence, which could no longer be used for another synthesis, suggest that a preparatively satisfactory insulin synthesis by this route is likely to be unattainable.

It still remains to examine the successive formation of the disulfide bridges by specific reactions for the preparation of asymmetric disulfides. Corresponding methods are known in principle, and have already been applied to model peptides having a partial insulin sequence[19].

Despite the uncertainty of this situation, studies on structure-action relationships have been started even for insulin. Though the need to use unsatisfactory synthetic routes has prevented the establishment of precise information about the biological action of insulin analogs, it is hoped that by exchange of amino acids, it will be possible to learn which amino acids or functional groups are essential to the action of insulin. The picture found for insulin is similar to that for oxytocin and vasopressin. Extensive replacement of amino acids has even less influence on the biological action, both quantitatively and qualitatively, than in the case of the hormones of the neurohypophysis. On the other hand, trifling modifications in the A chain, perhaps affecting the steric structure of insulin, are not permissible[20].

Insulin brings us very close to the old boundary between peptides and proteins; this boundary was passed for the first time with the syntheses of ribonuclease[21] and of ribonuclease S-protein[22]. However, the methods used in these cases were the same as those used in the synthesis of lower peptides, a further reason for paying more attention to the peptide nature of the proteins.

The trend toward increasingly bold syntheses of ever-larger peptides is unmistakable. In the very year in which the first synthesis was achieved, however, interest was also focused back on a group of lower peptides, *i.e.* the releasing hormones[23].

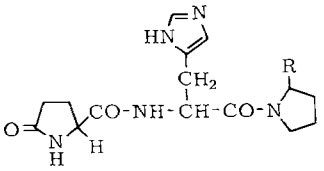
6. Releasing Hormones

The releasing hormones are formed in the hypothalamus, and migrate by a portal system into the anterior pituitary lobe, where they specifically effect the release of a hormone, each of these anterior pituitary hormones apparently being subordinate to a releasing hormone (and possibly also an inhibiting factor).

The importance of the releasing hormones is primarily in the diagnostic field. Just as the anterior pituitary hormones can be used to test the function of the target organs, *e.g.* of the gonads or of the adrenal cortex, it should be possible to test the function of the pituitary gland with the aid of the releasing hormones, and differential diagnosis of the types of cells involved in the production of a certain anterior pituitary hormone would then also be possible.

Releasing hormones may be of therapeutic use where subordinate anterior pituitary hormones obtained from animal material are inactive in man because of their species-specificity. The treatment of hormonal disturbances with releasing hormones would thus be equivalent to treatment with anterior pituitary hormones of the same species, provided that the anterior pituitary lobe is intact and that the releasing hormone lacks species-specificity. The structure of only one of these hormones, the thyrotropin-releasing hormone (TRH), is known at

present[24]. This substance is pyroglutamylhistidylprolinamide *(13)*. The story of the discovery of this hormone illustrates the unimaginable difficulties encountered in the investigation of this class of substances.



(13), R = $CONH_2$
(14), R = H

Even highly purified extracts from hundreds of thousands of hypothalami gave too little material for elucidation of its structure, and even this was not chemically uniform. The amino acids found in the hydrolyzate were regarded for a time as impurities, and no further thought was given to the peptide nature of these hormones.

It was only when the three amino acids histidine, proline, and glutamic acid were found in equimolar quantities in sufficiently pure preparations that the synthesis of the six possible isomeric tripeptides was started. These compounds were biologically inactive. However, the problem was nearer solution than the negative results indicated. When attempts were made to acetylate these peptides, Glu-His-Pro gave a product having a high TRH activity[25]. At the same time, it was deduced elsewhere[26] that pyroglutamic acid, which can be formed together with other products on acetylation of glutamic acid, is present. These observations finally led to the synthesis of pyroglutamylhistidylprolinamide, which was found to be identical with natural TRH[24]. The synthesis of this hormone and the determination of its constitution were thus achieved simultaneously.

The course of this structural elucidation presumably provides the model for the discovery of other releasing hormones, since all these compounds are isolable only in such small quantities, and are so difficult to obtain with the purity required for determination of their constitution, that confirmation by synthesis is necessary at a very early stage. Moreover, the availability of these hormones in sufficient quantities for diagnosis and therapy will also be dependent on synthetic preparation. The specificity of constitution of TRH is high. Even small changes in structure lead to loss of its biological activity. The amide group, however, is not essential to its action. Elimination of this group leads to a dipeptide-amide *(14)*, which, though less active, is just as specific as the natural hormone[27]. So far as we know, this dipeptide-amide is the first and at present the only dipeptide with such a strong and specific hormone action.

7. Closing Remarks

If one looks back on the work of past years, it is surprising at first to note that peptide chemistry in its present sense did not exist 20 years ago.

Though *Emil Fischer* laid the foundations in this field as early as the first decade of the present century, the superstructure was slow to assume its present shape. And though the discovery of the benzoxycarbonyl protecting group by *Bergmann* and *Zervas* in 1932 opened up a new phase in peptide synthesis, even in 1950 only a few naturally occurring dipeptides and tripeptides were known and had been synthesized.

Between 1944 and 1954, however, the analytical situation was made ripe for the purification, isolation, and constitutional elucidation of higher peptides, and *du Vigneaud* showed in 1953, with the synthesis of oxytocin[1], that the preparation of such substances in the retort was no longer a dream. This achievement broke the "spell", and the last decade has brought an undreamed-of advance in peptide chemistry, with the syntheses of corticotropin, insulin, glucagon, and calcitonin, and finally with the first synthesis of an enzyme and a releasing hormone.

The chemistry of peptides is methodically integrated with organic chemistry. Its objects, on the other hand, arise from biochemical problems. It thus constitutes one of the strongest and most active bridges between chemistry and biology, and it is surely reasonable to hope that medicine will participate to an increasing extent in this alliance.

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Lac Repressor

By Benno Müller-Hill[*]

Repressors are proteins that interact with inducers and operators to regulate the synthesis of enzymes in the cell. Lac repressor ensures that sufficient β-galactosidase is available to the bacterium Escherichia coli, depending upon the amount of lactose present in the culture medium. It has proved possible to isolate lac repressor from E.coli. The present progress report describes how these discoveries were made, as well as the formation and mode of action of the repressor.

1. Introduction

Some of the mechanisms which limit and control protein synthesis in bacteria have become known over the last few years. The bacterium *Escherichia coli* is particularly suited for such an analysis, since its chromosome is able to code for a total of only 3000 proteins. They are all formed according to the "central dogma" of molecular biology:

$$\text{DNA} \xrightarrow[\text{Transcription}]{} \text{RNA} \xrightarrow[\text{Translation}]{} \text{Protein}$$

Coli-DNA is transcribed in discrete pieces, covering one to twenty genes. The starting points, and presumably the stopping points, of transcription are fixed. The signals which indicate "start of transcription" have been called promoters; their base sequence, however, is so far unknown.

It is clear that only a few protein-synthesizing systems can be fully operative at one and the same time, otherwise the cell would be filled with unneeded proteins, grow more slowly, and lose out in evolution. An *E.coli* cell grown in the presence of glycerol, for example, needs enzymes to break down glycerol but has no need for the enzyme which breaks down lactose, β-galactosidase. It harbors only a few copies of this protein. But when grown for a few generations in the presence of lactose, the β-galactosidase level increases 500 fold: about two percent of the soluble protein become β-galactosidase. Similar drastic changes in amount of protein are found in many catabolic enzyme systems which break down sugars, amino acids, or lipids and many anabolic systems which synthesize amino acids or nucleic acid precursors.

In 1961 *Jacob* and *Monod* proposed a negative control system for the lactose system[1]. The biochemical realization of the negative control is simple: reversible steric hindrance of the process to be controlled is all that is needed. It can be exerted at any stage of the process. Intuitively, hindrance of the earliest step of the process of protein synthesis seems the most likely, but inhibition at later stages is also possible. *Jacob* and *Monod* proposed that the structural genes of the lactose system had a very efficient but negatively controlled starting site for transcription. For this, two separate control elements are needed: 1.) a diffusible gene product (the repressor), which is able to interact with a signal (the inducer), and 2.) a DNA site (operator), near the promoter, with which the repressor interacts so that the start or the progress of transcription might be blocked. The negative control by steric hindrance, and the distinction between the regulatory apparatus and the proteins to be regulated, are the most fundamental aspects of the model. This theory has been proved in all its elements to be correct.

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2. The i Gene and the Lac Repressor

2.1. The System

The lactose system has been very extensively studied over the last 25 years[2]. Figure 1 shows a schematic map of the lactose system in *E.coli*. The system consists of three closely-linked structural genes, z, y, and a, which code for β-galactosidase (z), lac permease (y), and transacetylase (a), respectively. The genes are transcribed in one molecule of messenger RNA (m-RNA)[1] and the direction of reading is from z to a[1,3]. Between the

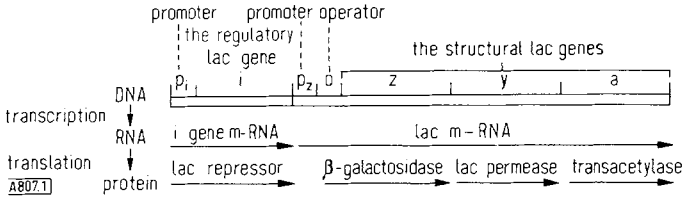


Fig. 1. The lactose system of *E.coli* DNA makes RNA, RNA makes protein – that is the dogma of molecular biologists. The regulatory i gene makes i gene messenger RNA which is translated into repressor protein. The structural lac genes make their own messenger RNA which is translated into three proteins: β-galactosidase, lac permease, and transacetylase. The promoter sites (p) are the starting sites of transcription. The operator site (o) is where synthesis of lac messenger is regulated. Fig. 1 to 3 are not drawn to scale.

starting site of transcription, the promoter (p_z), and the beginning of the z gene, lies a stretch of DNA to which the repressor binds in the absence of inducer (Fig. 2)[4]; this locus is called the operator (o). If repressor is bound to the operator, no transcription of the lac structural genes occurs. Promoter, operator, and the structural genes form one operon. The repressor is coded by a gene, the i gene, which attaches itself to the left on the promoter

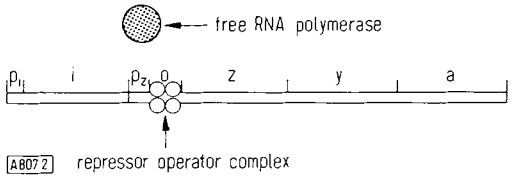


Fig. 2. Repression: Repressor sits on the operator DNA. The RNA polymerase molecules cannot sit properly on their starting site p (promotor) to make messenger RNA from the structural lac genes. There is also no RNA polymerase molecule on the promoter of the i gene; it is considered a bad promoter. Only rarely is transcription of the i gene successfully started. The cap protein [65] and cyclic AMP [64] are omitted in Fig. 2 and 3 (see below).

p_z. The i gene is also transcribed from left to right, so that its promoter (p_i) (starting site of transcription) is on its far left[5]. The sequence of all lac loci is thus p_i, i, p_z, o, z, y, a.

The i gene product, the lac repressor, inhibits the start and/or progress of the transcription of the structural lac genes in the absence of inducer. In the presence of an inducer, the repressor can no longer interact efficiently with the operator, and transcription can proceed (Fig. 3). The repressor exists in two forms: one form (R) is able to bind inducer (I) but no operator DNA (O); the other (R') can bind operator DNA (O) but no inducer (I). Since induction occurs rapidly, both forms must be in a rapidly forming equilibrium:

$$OR' \rightleftharpoons O + R'$$
$$R' \rightleftharpoons R$$
$$R + I \rightleftharpoons RI$$

This is the classical interpretation of the mechanism of induction. As we will see later, it is only partially true: ternary complexes (ORI) also play an important role.

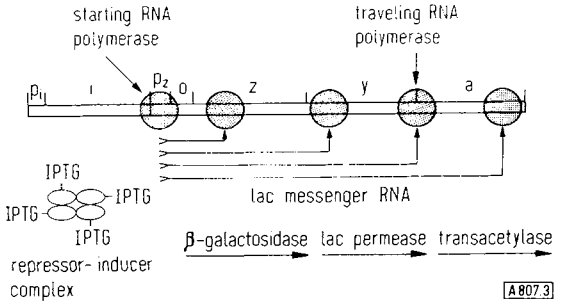


Fig. 3. Induction: Inducer has been added. All repressor molecules swim around as repressor-inducer complexes. This complex cannot bind to the operator site; the operator is free. An RNA polymerase molecule is about to start from the promoter site of the structural genes. It then begins its journey along the DNA and transcription has started. Before the polymerase reaches the end, other polymerase molecules hop on. The long threads of the transcribed messenger RNA hang from the RNA polymerase molecules. These in turn make the three structural proteins.

2.2. Properties of the Wild-Type i Gene Product: Specificity of Induction.

Lactose enhances the rate of β-galactosidase synthesis in *Escherichia coli*. The presence of the product of the y gene (lac permease) is necessary for the entry and accumulation of lactose into the cell[6]; that is, a y^- mutant cannot be induced by lactose. After the lactose has entered the cell, it is still unable to induce[7]; it has first to be converted into the real inducer by the few molecules of β-galactosidase present in the uninduced cell. β-Galactosidase not only breaks down lactose into galactose and glucose, but also transfers the galactose moiety of lactose to suitable acceptors[8]. Such acceptors can be molecules having aliphatic hydroxy groups. Among these

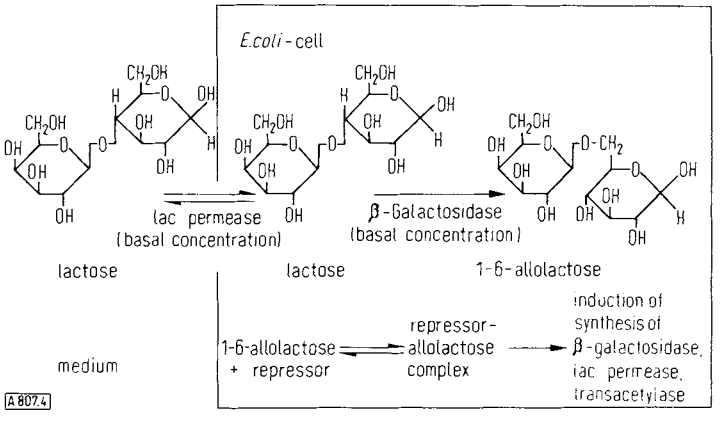


Fig. 4. The induction process with lactose: Lactose has first to enter the cell. This only happens in the presence of lac permease. There are always a few molecules of permease around, even in uninduced cells. Now it has to hit a β-galactosidase molecule. Uninduced cells contain several β-galactosidase molecules. Here it is either hydrolyzed or converted into one of the various lactose isomers (1-2, 1-3, 1-6 allolactose). Only the 1-6 allolactose is able to bind to lac repressor.

transfer products, the 1–6 lactose isomer (allolactose) and galactosido-β-D-glycerol are active as inducers of the lac system[7,9]. The other lactose isomers, which are also formed, have been tested and have been found inactive. The whole chain of events is depicted in Fig. 4.

To circumvent this double complication in the laboratory, galactosides have been synthesized which can enter the cell in the absence of permease, which are inducers without prior interference from β-galactosidase, and which are not hydrolyzed by β-galactosidase[10,11]. The most effective of these synthetic sugars is isopropyl-1-thio-β-D-galactopyranoside (IPTG). It induces at the lowest concentration of all known lac inducers, and leads, under saturating conditions, to the highest maximal rate of β-galactosidase synthesis.

Any analysis of the concentration dependence of induction implies that the concentration of the inducer *inside* the cell is known. The inside concentration does not necessarily equal the concentration in the medium, since the inducer might be accumulated by the cell. Such is the case[12] with 1-β-D-galactosidoglycerol, which for some time was thought to be the most effective inducer of the lac system[7].

Among the synthetic sugars, a whole set has been found which are not only non-inducers, but also induction inhibitors[9]. The most prominent member of this class of anti-inducers is *o*-nitrophenyl-β-D-fucopyranoside (ONPF). It is reasonable to think that it acts by binding to the form of repressor which sticks to the operator[13], thereby stabilizing the operator-repressor complex. It isn't surprising that several sugars have been found which fall into both classes: they induce weakly and they inhibit induction weakly. They have been called paradoxical compounds[14]. The structural differences between inducers, anti-inducers, and inert compounds are rather small (see Table 1).

Table 1. Specificity of induction and antiinduction.

Inducers:
1-6-*O*-β-D-galactopyranosyl-D-glucose [7,9]
isopropyl-1-thio-β-D-galactopyranoside [11]

Antiinducer:
o-nitrophenyl-β-D-fucopyranoside [9]

Weak inducer and weak antiinducer:
p-aminophenyl-1-thio-β-D-galactopyranoside [14]

Inert analogs:
1-4-*O*-β-D-galactopyranosyl-D-glucose (lactose) [7,9]
p-nitrophenyl-β-D-fucopyranoside [9]
o-nitrophenyl-1-thio-β-D-fucopyranoside [9]

2.3. Mutants of the i Gene

The i gene is characterized by a large variety of mutants with different phenotypes (Table 2). They fall into two main classes: mutants that no longer repress, and mutants that have altered inducer-binding capacity.

Mutants of the first class, in which the i gene product is unable to bind efficiently to the operator, are constitutive, that is, they produce under all circumstances

Table 2. Mutations in the i gene.

Genotype	Biological Phenotype (i z^+y^+)	Molecular Phenotype	Ref.
i^+	Wild-type; inducible; grows on lactose	About 10 molecules of normal repressor per cell	[1]
i^-	Constitutive; grows on lactose	The mutated repressor is unable to bind to operator and to stop transcription of the lac structural genes	[1]
i^{-d}	Constitutive; transdominant; grows on lactose	i^{-d}Repressor is able to form mixed i^+i^{-d} oligomers; they are unable to bind to operator	[15, 16]
i^s	Normal basal level of β-galactosidase; is not induced by low concentrations of inducer; transdominant over i^+; does not grow on lactose	Repressor binds to operator but only badly to inducer	[23]
i^r	Constitutive; β-galactosidase synthesis is repressed by some galactosides	Not well analyzed	[20, 21]
i^{TL}	Constitutive at high temperature; wild-type at low temperature; grows on lactose	Repressor is temperature-sensitive	[22]
i^{TSS}	Constitutive at high temperature; wild-type at low temperature; grows on lactose	Repressor subunits are temperature-sensitive; tetrameric repressor is stable	[22]
i^i	Induced by subnormal IPTG concentrations; grows on lactose	Binds IPTG tighter	[16]
i^q	Wild-type; grows on lactose	About 200 molecules of normal repressor per cell	[16]
i^{superq}	Wild-type; grows on lactose	About 1000 molecules of normal repressor per cell	[19]

("constitutively") large amounts of β-galactosidase[1]. They are called i^- (the minus sign signifies the absence of functional i gene product). Two classes of such i^- mutants have been found: recessives[1] and transdominants (i^{-d})[15,16]: "recessive" means that the introduction of a second functional i^+ gene into a cell which already carries an i^- gene leads to repression. The new i^+ gene produces functional repressor which is not influenced by the existence of possible products of the i^- gene; "transdominant" means that the constitutive character of the i^- dominates over the i^+ character of the other i gene. To the recessives belong: a) the nonsense i^- mutants[17,18], in which only the amino terminal piece of the i gene product is made; b) some, but not all, i gene deletions (mutants whose i gene is missing either in part or completely), and c) some, but not all missense mutations, in whose i gene product one amino acid is exchanged for another. Among the transdominants, not only three missense mutations[15,16] but also three deletions[19], all cutting into the amino terminal end, have been found. Their behavior can be explained by negative complementation[16] (*i.e.* the formation of mixed i^+i^{-d}oligomers): the i^{-d}character of one subunit "spoils" all the "good" i^+ subunits. This is quite possible, since normal repressor has been shown to be a tetramer (see below). Further, i^{-d} repressor could also bind to operator without repressing.

There are also i mutants in which the repressor binds to the operator after the addition of various synthetic sugars such as IPTG, ONPF or TDG (thiodigalactoside)[20,21]. They have been called i^R. In most of these cases, repression is not quantitative.

Two classes of temperature-sensitive i^- mutants have been isolated[22]: mutants in which the i gene product itself is temperature-labile (i^{1L}), and mutants in which a precursor (presumably the subunit) of the repressor is temperature labile (i^{TSS}).

There are a variety of mutants in which IPTG or lactose do not induce at the usual concentration. The phenotype of such mutants is lac^-; that is, they cannot grow on lactose. They are transdominant. They map in the i gene and are called i^s[23]. They are rather rare; only 0.4% of independent lac^- has this genotype. One might assume that the binding of inducer to repressor has become weaker, or, less likely, that the binding is still strong but that the repressor binds to the operator even in the presence of inducer. Revertants of these mutants which can grow on lactose are almost exclusively i^- or o^c (see below), since it is much easier to destroy the i gene by mutation than to revert just the one base pair which made an i^s from the original i^+. A rare mutant has been isolated (i^t) in which the binding of repressor to IPTG is tighter than normal[24].

Only a few of the i^- mutants mentioned have been mapped by three factor crosses[15]. Deletion mapping of sixteen i^s and two i^{-d} mutants has been carried out[25] (see Fig. 5).

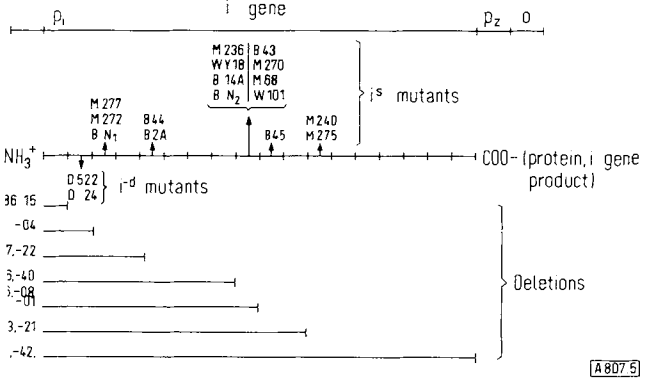


Fig. 5. Genetical map of the i gene: 16 i^s and 2 i^{-d} mutants have been mapped. They have been ordered with 18 tryp-TonB-i deletions in the transposed lac strain. The deletions X8600 are from the collection of *J. Miller*. Strains No. 68, 101, 236, 240, 270, 272, and 275 are from the collection of *B. Müller-Hill*. Strains No. N1, N2, 2A, 14A, 43, 44, and 45 are from the collection of *S. Bourgeois*. Strain y18 is from *C. Willson* and strains 24 and 522 are from *J. Davies*. The mapping has been done by *M. Pfahl*. Details will be given elsewhere[25].

Although the number of mutations and deletions investigated is too small in order to make definite conclusions there are indications that the i^{-d} and i^s mutations occur in clusters at definite sites of the genome. One might hope to obtain through mapping of such mutations and sequence analysis of the corresponding repressor (see below) a picture of the active sites of the repressor.

2.4. Mutants of the i Gene Promoter

Starting from a temperature-sensitive i gene mutation of the i^{TSS} type[22], a mutation of the i gene has been isolated which overproduces lac repressor[16]. It has been called i^q (q for quantity). The overproduction was at first estimated to be about tenfold. This was based on data obtained from the original strain that overproduced temperature-sensitive repressor. Since then, the TSS mutation has been crossed out, resulting in a strain that overproduces presumably wild-type repressor[26]. Recent data using this strain suggest that the increase in repressor is more likely twenty fold. Starting from this strain, it has been possible to isolate an even better overproducer[26]. This strain, called i^{superq}, makes five to ten times more repressor than the i^q strain (see Table 3). These strains have been used to isolate enough repressor (4g) for a sequence analysis (see below). The q mutation has been mapped at the left side of the i gene[19].

Table 3. Lac repressor levels in various strains.

Genotype	lac repressor molecules per cell	
	i gene on the chromosome	i gene on the phage [b]
i^+	10	300
i^q [a]	200	6000
i^{superq} [19]	1000	20000

[a] i^q is the strain overproducing wild-type repressor. The originally[16] present TSS mutation has been crossed out[19].
[b] "On the phage" means after heat induction of cells carrying the prophage $\lambda h80c_{1857}t68dlac$[16], a phage in which part of the phage genome is replaced by the lac genes.

2.5. Changing the Number of Copies of the i Gene in the Cell

E.coli contains, under normal conditions, only one copy of each gene per chromosome. It has been known for a long time that doubling the number of copies of uncontrolled genes leads to a doubling of the gene products in question[22]. Strains having three sets of lac genes can be constructed[27] by using lac transducing phage. They yield, as expected, an approximately threefold increase of the i gene product. An elegant way of introducing many copies of one particular gene into *E.coli* is to use a multiplying specific transducing phage which carries this gene. Such a phage is available for the lac system[27]. It has been made more useful by the introduction of two additional mutations: one which allows the multiplication of the phage to start by means of a short heat treatment of the bacteria (the phage has a temperature-sensitive repressor; the mutation is called c_{1857}), and another mutation which prohibits lysis of the bacterial cells after the phage is induced (the nature of the lysis inhibition is not clear; the mutation is called t68[28]). The use of this phage yields a 30 fold increase in amount of repressor made[16] (see Table 3).

2.6. Consequences of the Low Amount of Repressor in Wild-Type Strains

The repressor is made in only a few copies per cell. An accurate estimate of the amount is difficult since repressor cannot be determined accurately in the crude extract of the wild-type strain. A reasonable estimate is that there are about 10 molecules present per cell[24]. A likely explanation for the low amount of repressor is that the promoter of the i gene (its starting site for transcription) is very inefficient[16]. One or two copies of i gene messenger RNA per division cycle could be sufficient for the amount of repressor found, since one messenger RNA molecule can be translated several times before it decays. The assumption of a slow rate of i gene messenger synthesis can be used for the interpretation of several phenomena:

It has been observed that β-galactosidase is made at a fast rate over 60 minutes if a male (F' or Hfr) i^+z^+ strain is allowed to mate a female strain harboring a lac deletion[29] (Fig. 6). The β-galactosidase z^+ genes are no

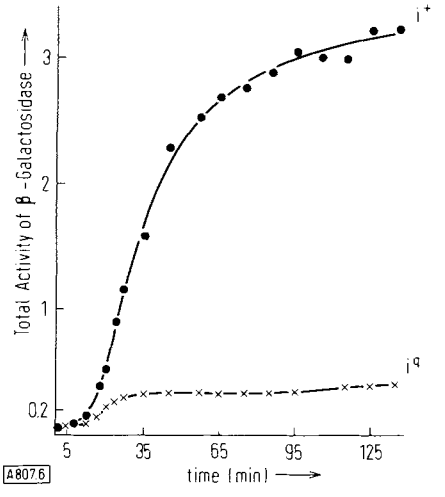


Fig. 6. Onset of repression in a mating experiment: The experiment which had been already performed with ambiguous outcome with a $F'i^{qTSS}$ male [16] has been repeated with an $F'i^{q+}$ male. At time $t = 0$, Sm^s male cells growing exponentially at 37 °C and carrying either the $F'i^+z^+$ or the $F'i^qz^+$ episome were mixed with a two fold excess of Sm^r female cells carrying the RV lac deletion. After 10 minutes of further growth at 37 °C in the casamino-acid-M56[10] glycerol medium, mating was interrupted by vortexing and adding of 30γ/ml of sodium dodecyl sulfate. Streptomycin (250γ/ml) was added to stop further growth of the male cells. Samples were withdrawn at 10 minute intervals, to measure β-galactosidase[9]. The efficiency of transfer of the lac character was determined by plating. It was between 15 and 20%. The β-galactosidase levels are given in arbitrary units normalized to equal transfer after subtraction of a male cell blank. ·–·–· $F'i^+z^+$ males, ×–×–× $F'i^qz^+$ males. The data have been taken from the dissertation by *M. Pfahl*. Universität Köln.

longer repressed after they have been transferred into the female cell. They function constitutively for quite a while in the new environment. Before the first i gene messenger RNA is made, β-galactosidase is produced at maximal speed. The synthesis of repressor messenger RNA occurs statistically at different times in different cells, but after a certain time half of the cells should have had one i gene messenger RNA made, which would make several repressor copies within a few minutes. This should lead to an almost complete shut-off of β-galactosidase synthesis in these cells. If the logarithm of the relative rate of β-galactosidase synthesis is plotted against time a straight line is obtained (Fig. 7). On inspection of the data for the wild-type F'lac $i^+z^+y^+$ we find that the decay of the rate of β-galactosidase synthesis is exponential over 60 minutes. After 24 minutes the rate has fallen by a factor of 1/e. If our interpretation is correct this means that one i gene messenger is made every 24 minutes. The existence of the i^q mutation gives us an internal control for the experiment. If the i^q mutation is a promoter mutation, that is, if it increases the occurrence of the start of transcription of the i gene, we can make a clear prediction for a similar experiment

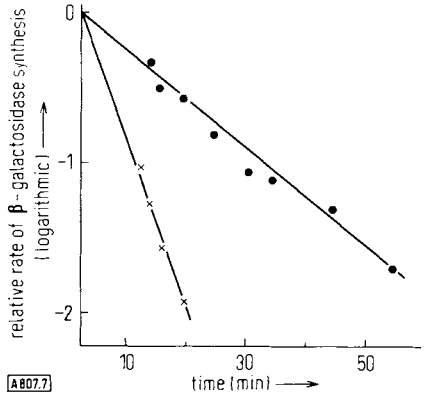


Fig. 7. Onset of repression in a mating experiment: The data from Fig. 6 have been replotted. The logarithm of the rate of β-galactosidase synthesis (in arbitrary units) is plotted against time. The straight lines indicate exponential decay of this capacity (·–·–· $F'i^+z^+y^+$, ×–×–× $F'i^qz^+y^+$). We interpret this as an indication of rare i gene transcription in the wild-type, and more frequent transcription in the i^q mutant[16].

using an $F'i^qz^+y^+$: the decay of the rate of β-galactosidase synthesis should be correspondingly faster. Figure 6 contains the experimental data; Fig. 7 shows that in the case of the i^q the rate of β-galactosidase synthesis decays at least 3 times faster than in the wild-type. This would indicate that the frequency of transcription is three times higher in the i^q than in the i^+ strain. One might wonder why it is not found to be even higher, since 20 times more repressor is made – at the moment we can offer no simple explanation.

Methyltryptophan was used in order to stop protein synthesis in such a mating experiment and thus to test whether the assembly of the repressor precursors takes a long time[30]. The same exponential decrease in the rate of β-galactosidase synthesis was observed as under normal conditions. It may be concluded that it is actually the process of m-RNA synthesis which is rate-determining, and that the assembly of the repressor is rather fast[16].

The small amount of repressor made in wild-type cells is the cause of another interesting phenomenon: escape synthesis of β-galactosidase after UV[31] or heat[32] induction of lac transducing phage. The replicating lac genes $i^+o^+z^+y^+$ escape repression control: β-galactosidase is synthesized constitutively after phage induction. It has been concluded that escape synthesis is due to the lack of sufficient repressor to titrate all operators of the replicating DNA. Particularly clean results have been ob-

tained using the heat-inducible $\lambda c_{I857}h80t68dlac$ phage[32]. Escape synthesis occurs for exactly ten minutes, and then stops completely while phage DNA replication proceeds. If one uses a phage which carries the i^q gene, no escape synthesis is observed. Enough repressor is synthesized at all times to titrate all operators.

Another consequence of the existence of only a few repressor molecules per cell is the time curve of β-galactosidase production after heat induction of an i^{TTS} strain[22]. The "turning-on" of β-galactosidase synthesis by a shift to high temperature has been called heat induction. The repressor already formed in the i^{TSS} strain seemed to be stable at high temperature whereas no new functioning repressor seemed to be assembled under these circumstances. If an i^{TSS} strain is grown for several cell generations at low temperature, and if the temperature is then raised to 43 °C, β-galactosidase synthesis begins to accelerate before the cells have doubled. The first explanation of this phenomenon has been that since already-formed i^{TSS} repressor was stable in the absence of growth it was unstable in the presence of growth. Under growing conditions, it was supposed to have a halflife of 1/10 to 1/5 of a generation[22]. A more plausible explanation is that the i^{TSS} repressor is somewhat temperature labile itself: at very low repressor levels, small differences in repressor concentration in different cells can lead to vastly different rates of β-galactosidase synthesis. Two lac operators and two repressor molecules lead to complete repression, whereas two lac operators and one repressor allow one lac promoter to function at optimal speed. A Poisson distribution would describe the situation. According to this interpretation, rather soon after the temperature shift some cells would contain less repressor than operator. In order for the proposed mechanism to be proven, the inhomogeneity of the cells in regard to β-galactosidase content has to be demonstrated experimentally; this has not yet been done.

2.7. The Nature of the i Gene Product

At the time when the Jacob-Monod model was published, and the existence of messenger RNA had just been proved, it seemed quite reasonable that the repressor might be a nucleic acid[35], that is, presumably the messenger RNA from the i gene. This was actually proposed on the basis of a faultily-interpreted mating experiment in which chloramphenicol was supposed to have completely stopped the synthesis of new protein, but in which new repressor seemed to have been made[34]. On the other hand, it was difficult to believe that an RNA molecule should be able to interact specifically with a small molecule such as IPTG. The known facts about inducer specificity[7,9,10] suggested that the repressor was a protein. The first experiment which made this seem rather likely was the finding of temperature-sensitive i gene mutants[22]. In the two types of temperature-sensitive mutants which were found, either the repressor itself was temperature-labile, or the precursor of the repressor was temperature-labile. Since temperature-sensitive RNA molecules were not known at the time, it made good sense to assume that the repressor was a protein. The same mutants also gave excellent proof of the fact that the inducer binds directly to repressor: IPTG influences the stability of the temperature-sensitive repressor[22]. Furthermore, from the concentration dependence of the heat lability of the repressor in the i^{TSS} strain, it was concluded that the repressor might be a tetramer or another oligomer[22]. More rigorous proof of the protein nature of the repressor was given a few years later. The i^- mutants obtained from i^{s}[17] or i^{+}[18] strains were found to be suppressed by nonsense suppressors. Since nonsense suppression acts on the level of translation by prohibiting chain termination in the nonsense codon, this clearly showed that the translation of the i gene messenger RNA was necessary for the synthesis of functioning repressor.

2.8. *In vitro* Tests of the Lac Repressor

Two types of tests are available for the assay of lac repressor: they measure its binding to inducer IPTG[24,36] or to lac operator containing DNA[37,38]. A sensitive way to determine small amounts of repressor is by equilibrium dialysis with ^{14}C labeled IPTG[24]. The extract to be tested is transferred to a dialysis sac and dialyzed against a 10^{-7} molar solution of ^{14}C labeled IPTG. After equilibrium is reached an equal volume is taken from the outside solution and from inside of the sac, and counted. A more elegant and faster method makes use of the fact that the lac repressor binds to nitrocellulose (millipore) filters, and when bound there, binds IPTG tightly[36]. The latter method is limited by the amount of protein that can be put through the filter: the filter becomes saturated at about 10 to 100 micrograms of protein. Other methods, such as precipitation of the complex with ammonium sulfate[39] (the Farr test from immunology[40]) and phase partition have been used[21].

The binding of lac repressor to lac operator (see below) can be followed rather laboriously using glycerol gradients with $\lambda h80dlaco^+$ DNA and ^{35}S labeled repressor[37] or, more easily, using the filter-binding technique with cold repressor and ^{32}P labeled DNA[38].

2.9. *In vitro* Tests of Mutant Lac Repressor

The original test for lac repressor[41] relied on the IPTG binding capacity of the repressor[24]. The proofs of the isolation of the lac repressor relied on the use of i gene mutants. The physico-chemical behavior of the repressor has to agree with the predictions of the properties of mutants. The simplest correlates are negative ones. Thus one would expect the absence of IPTG binding material in extracts made of strains which harbor i gene deletions. IPTG binding was indeed found to be absent in several i deletion strains, but since in some of these strains the deletion passed the borders of the i gene, this was not a very good control. A more rigorous control was the absence of IPTG binding material in extracts from one i^- nonsense mutant, since one would probably not expect a repressor fragment to bind IPTG. (Later

studies [see below] showed that some deletions which only cut small pieces from the amino-terminal end or from the carboxy-terminal end, still have IPTG binding capacity[19].) One might also expect i^s mutants not to exhibit good IPTG binding. Indeed, in the one i^s strain which was originally studied, no binding was found[24].

All these proofs are strictly negative; better proof that the IPTG binding was caused by the i gene product was provided by the following positive correlations between the extract behavior and the mutants genotype: the IPTG dissociation constant was found to be two times smaller in an extract made from the i^t strain than in one from wild-type[24]. Another positive correlation was found with temperature-sensitive i^{TL} and i^{TSS} mutants[42]. As expected, the IPTG binding activity of the i^{TL} extract was more heat-labile than in the wild-type. The i^{TSS} extract was also found to be heat-labile. This was somewhat unexpected at the time; it now actually serves for the interpretation of the growth instability of the repressor (see above). The binding of lac repressor to operator (see below) gives the final proof that the i gene product is the repressor. Recently, the weakened inducer binding of i^s repressors has been demonstrated in a convincing manner[43]: the stronger the i^s character the weaker the interaction with IPTG *in vitro*.

2.10. Purification of the Lac Repressor

In most purifications of the lac repressor, only IPTG binding has been followed. The repressor is very stable in this respect. Operator binding, on the other hand, tends to disappear rapidly during purification of the lac repressor. It is likely, but not proven, that the repressor is simply very labile and denatures partially during the purification procedure, like many other allosteric proteins. But it is not excluded that an essential part of the repressor is lost during the purification procedures. Pure lac repressor can be obtained in two steps using the extract from a strain carrying the i^q gene[44] on the $\gamma h80c_{I857}t68dlac$ prophage. The phage is induced to multiply by a short heat treatment of the bacteria. The i^q genes which are multiplied with the phage then make about 1% of the soluble protein of the bacteria repressor. The bacteria are centrifuged and frozen for storage. They lyze when they are put into buffer (pH = 7.6). The debris are spun down. Ammonium sulfate precipitation between 20 and 30% and chromatography on phosphocellulose are sufficient to obtain pure repressor (Table 4). Chromatography on DEAE cellulose and on sephadex has also been used successfully[36,46]. In the crude extract of the heat-induced nonfrozen phage-carrying i^q strain the repressor has a sedimentation constant of 7S. It has a tendency to aggregate during purification and to precipitate out of solution[44,36]. Our investigations show that the sedimentation constant of 7S is not appreciably changed if repressor is centrifuged in the presence of 10^{-3} M IPTG or 10^{-3} M ONPF. The molecular weight of the 7S species has been determined by equilibrium centrifugation to be 150000[45]. In electrophoresis on sodium dodecyl sulfate (SDS) acrylamide gels, a single band is seen. The location of the band indicates a molecular weight of 39000[45]; the molecular weight of the monomer, calculated from the amino acid analysis, is 40000[46]. The form in which the repressor seems to be most stable is tetrameric. But under extreme conditions, such as after freezing, freeze-thawing, in very high tris or salt concentrations, monomers, dimers, and higher aggregates have been observed[46]. The amino acid composition is normal: the repressor contains all amino acids normally occurring in proteins[46] (Table 5). It is an acidic protein (the isoelectric point is 5.6)[45].

Table 4. Purification of lac repressor from 100 g frozen cells ($\lambda h80c_{I857}t68dlaci^q$)[44].

		Specific activity [a] (%mg^{-1}ml^{-1})	Recovery (%)	Total amount of repressor (mg)
Step I	Total extract	14	100	61
Step II	Supernatant after first ammonium sulfate precipitation (0–15%)	19	98	60
Step III	Dialyzed ammonium sulfate precipitate (15–33%)	112	88	54
Step IV	Phosphocellulose chromatography: peak	1 300	54	33

[a] The specific activity of the lac repressor is determined by equilibrium dialysis against ^{14}C labeled IPTG[24]. Per cent/mg/ml means excess of IPTG inside the dialysis sac expressed in per cent, divided by the protein concentration (mg/ml).

Table 5. Amino acid composition of lac repressor (i^q) from *E.coli*.

Amino acid	µmole/100 µmole	Calculated amino acid residues per 40 000
Lysine	3.67	13
Histidine	1.69	6
Arginine	4.80	17
Aspartic acid	9.04	32
Threonine	5.37	19
Serine	7.34	26
Glutamic acid	12.43	44
Proline	3.95	14
Glycine	7.34	26
Alanine	11.58	41
Cysteine [a]	0.58	3
Valine	8.19	29
Methionine	2.25	8
Isoleucine	5.65	20
Leucine	10.73	38
Tyrosine	2.26	8
Phenylalanine	2.26	8
Tryptophan [b]	0.56	2

[a] Determined as cysteic acid.
[b] Data from enzymatic and alkaline hydrolysis.

Chemical analysis of pure repressor has provided no evidence for the presence of reducing sugar or of nucleic acids[44]. The ratio of absorption at 280 nm to that at 260 nm has been found to be as high as 1.8 in pure tetramer preparations (Table 6). In aged preparations, where the repressor has started to aggregate, the OD ratio can drop appreciably due to light scattering and thereby falsely suggest the presence of nucleic acids.

The number of IPTG binding sites has been accurately determined (Fig. 8). There is exactly 1.0 binding site per subunit[46].

Table 6. Properties of lac repressor (i^q) from *E.coli*.

		Method of determination	Ref.
Rel. molecular weight	150000	High speed equilibrium method	[45]
Rel. molecular weight of subunit	40000	Dodecyl sulfate polyacrylamide gel electrophoresis. Amino acid analysis	[45, 46]
Sedimentation value tetramer monomer	 7.2 2.7	Glycerol gradient	[24, 36, 46]
Isoelectric point	pH 5.6	Isoelectric focusing	[45]
DNA content RNA content	< 1.2% <0.2%	Dische reaction Orcinol reaction	[46]
Binding sites for IPTG per mol. weight 150000	4.2	Equilibrium dialysis	[46]
Binding constant for IPTG in TMS 4°C	1.8×10^{-6}M	Equilibrium dialysis	[24, 36, 46]
$O.D._{280}$ 0.1%, 1 cm	1.38		[46]
$O.D._{280} : O.D._{260}$	1.8		[46]
Amino terminus Carboxyl terminus	Methionine Lysine	DNP-, Dansyl-method, Edman degradation Carboxypeptidase B, Hydrazinolysis	[45, 46] [46]

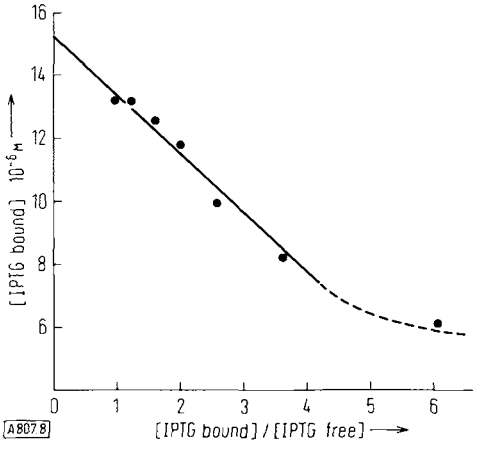


Fig. 8. Inducer binding sites of the lac repressor. Bound IPTG is plotted against bound IPTG over free IPTG. The concentration of repressor in this experiment was 3.6×10^{-6}M. The curve extrapolates to four sites per one repressor molecule of a molecular weight of 150000[46].

Tryptic fingerprints (*i.e.* paper chromatograms of the protein after cleavage with trypsin) have been made[46]; they give the approximate number of spots (29) one expects from the arginine and lysine content (30). This, together with the genetical data, strongly suggests that the repressor consists of four identical subunits. Methionine has been shown to be the N terminal amino acid[45,46]; the sequence at the C terminal is Arg-Lys[46].

2.11. Properties of Repressor Isolated from Various i Gene Mutants

Only a few i gene mutants have been analyzed for the biochemical or physical properties of their repressors. Rather surprisingly, it has been found that many i^- mutants still contain IPTG binding capacity. Such is the case with one i^{-d} mutant (i_{24}^{-d})[46], one transdominant deletion[19,46], which cuts from the tryptophan operon into the first part of i, and the deletion LI[19], which cuts from the carboxy-terminal end of the lac repressor into the lac promoter. The protein in the latter case has been isolated and the molecular weight of the subunit has been determined by SDS acrylamide gel electrophoresis to be 38000[19].

2.12. Dominance of the Lac i Gene Mutants

When *Jacob* and *Monod* proposed their model, the dominance relationship of the i gene seemed to be simple and clear. Presence of the repressor (i^+) was dominant over the absence of repressor (i^-)[1]. Presence of a mutant repressor, which was unable to interact effectively with inducer (i^s), was dominant over both i^+ and i^-[23]. The finding of transdominant i^{-d} mutants posed the first problem[15,16]. Do they act by negative complementation (by forming mixed oligomers which are unable to bind to the operator) or does their repressor still bind to the operator but remain unable to stop transcription? If, as seems most likely, negative complementation is the explanation for the dominance, the subunits of the i^{-d} repressor must aggregate very slowly. Since repressor mRNA is only made every twenty minutes no complementation could otherwise occur. (We assume that the tetramers, once they are formed, are stable and cannot exchange subunits.)

The existence of mutants which overproduce wild-type repressor leads to further complications: i^q is dominant over i^s[16]. The simplest explanation is certainly complementation, that is, the formation of normally functioning mixed oligomers between i^s and i^+ repressor subunits. The halflife of free i^s repressor subunits can be rather short, since in the i^q strain lac messenger is made every six minutes. The mixed oligomers can be induced by IPTG to fall off the operator.

All the dominance relationships are summarized in Table 7.

Table 7. Dominance relationships.

Genotype	dominant over	Ref.
i^+	i^-	[1]
i^s	$i^+; i^-$	[23]
i^{-d}	i^+	[15, 16]
i^q	$i^s; i^{-d}$	[16]

Table 8. Repressor operator interaction. The bacteria were grown in minimal medium M56 [10] with glycerol at 37 °C. β-Galactosidase was determined as in [9].

Genotype	Specific activity of β-galactosidase
$i^+o^cz^+$	2000
$i^+o^cz^+/F'i^+o^+z^+$	1200
$i^+o^cz^+/F'i^qo^+z^+$	300
$i^+o^cz^+/F'i^{superq}o^+z^+$	130
$i^+o^+z^+$	15

3. The Operator and the Mode of Action of the Repressor

3.1. Mutations of the Operator Locus

Genetic analysis shows that the product of the i^- gene reacts in *trans* with the operator[1]: it sits not only on operators which lie next to the i gene but also on distant lac operators such as on an F′ or a prophage. The operator is characterized by operator constitutive mutations (o^c). They are *cis* dominant mutations in which the repressor-operator interaction is weakened: the synthesis of β-galactosidase (in *cis:* that is from the z gene which is *directly* connected with the operator) is no longer one thousand fold repressed; it has become partially constitutive. By the addition of inducer it can be fully induced. No operator constitutives have been found so far which totally abolish repression. The strongest o^c's are still eight fold repressed. It has been claimed[47] that all o^c mutants are deletions, but this is questionable, since the most important property of deletions, their non-revertibility, cannot be easily checked. The frequency of occurrence of o^c's, after the use of specific mutagens, has also to be interpreted cautiously since the alleged o^c's have been isolated from i^si^s diploids, and complications such as the existence of transdominance or increased homozygosis after mutagenesis will obscure the results.

3.2. Estimate of the Binding Constant between Repressor and Operator from Data Obtained *in vivo*

The introduction of an $F'i^+$ episome (F′ = an independently replicating piece of DNA consisting of an F factor and bacterial DNA, in this case the lac genes) into a cell carrying an $i^+o^cz^+$ genotype reduces the rate of operator constitutive β-galactosidase synthesis by a factor of 2 to 2.5[1]. Since the repressor level is doubled by the introduction of a second i gene, one can state that the speed of β-galactosidase synthesis varies inversely with the first power of repressor concentration[22]. We have tested this further by the introduction of an $F'i^q$ into the same $i^+o^cz^+$ strain. The level of repressor then increases ten to twenty fold; the β-galactosidase level decreases by a factor of 7 (see Table 8). This indicates that there is a simple mass action relationship between repressor and operator.

$$R + O \rightleftharpoons RO$$

$$\frac{[R]\ [O]}{[RO]} = K_o$$

If we make the reasonable assumption that the synthesis of β-galactosidase is proportional to the concentration of free operator[22], the concentration of free operator has to decrease as the concentration of repressor increases. This is also true for the wild-type o^+ basal level. That is, the basal level goes down by a factor of two, if an $F'i^+o^+z^-$ is introduced into an $i^+o^+z^+$ strain[48]. Now we might calculate the binding constant between repressor and operator: the volume of an *E.coli* cell is 0.7×10^{-12} cm^3; Avogadro's number is 6×10^{23}. This means that the solution of one molecule in one *E.coli* cell is about 10^{-9} molar. In a normally dividing *E.coli* cell, the lac operator concentration would be 2×10^{-9} molar, and the lac repressor concentration (assuming 10 molecules/cell) 10^{-8} molar. If one assumes that the observed ratio 1 : 1000 in β-galactosidase levels between the uninduced and the induced state is totally due to repression, then the concentration of free operator in an uninduced cell should be 2×10^{-12} M. The concentration of operator-repressor complex practically equals the concentration of total operator, 2×10^{-9} M. The concentration of free repressor is also practically unchanged, 10^{-8} M. From these data we can calculate the binding constant:

$$K_o = \frac{[R]\ [O]}{[RO]} = \frac{10^{-8} \times 2 \times 10^{-12}}{2 \times 10^{-9}} = 10^{-11}\ \text{M}$$

3.3. Determination of the Binding Constant of the IPTG-Repressor Complex

The dependence of the induction on the concentration of the inducer in an $i^+o^cz^+y^-$ and an $i^+o^+z^+y^-$ strain gives a direct measure of the binding constant of the inducer towards repressor[23, 24]. The dependence of the inducer concentration is not first order, but third order. If we disregard this for the moment, we have the following two alternative models. Either it takes just the same amount of IPTG to double the basal level in the o^+ as in the o^c, or it takes the same amount of inducer to get half maximal induction in both strains. Since the former is true[23], the following equation holds:

$$K_i = \frac{[I]\ [R]}{[IR]}$$

If we assume that the speed of β-galactosidase synthesis is proportional to free operator, it follows directly that the inducer binding constant is numerically equal to the

concentration of IPTG that is necessary to double the basal rate in an i^+o^+ or an i^+o^c strain; that is, K_i equals 2×10^{-6} M. The binding of repressor to IPTG has been determined *in vitro*. Binding was found to be anticooperative with repressor from i^+ cells; pure i^q repressor showed no cooperativity in binding to inducer. The experimental conditions (temperature, *etc.*) do not correspond to the *in vitro* conditions; still, how can this be reconciled with the third order kinetics of induction? No quantitative theory which accommodates all the facts has been worked out. It suffices to say here that one IPTG molecule bound to the repressor might be enough to weaken its binding to the operator sufficiently to lead to induction.

3.4. *In vitro* Measurements of the Repressor-Operator Binding

The binding of repressor to operator DNA has been measured using two assay systems. One uses centrifugation of the complex through glycerol gradients[37], the other adsorption of the complex on nitrocellulose (millipore) filters[38]. DNA from lac o^+ transducing phages has been used as a source of operator DNA. This has the advantage that 70 times less DNA has to be used than would be the case if one used *E.coli* DNA. Moreover, the phage DNA is uniform in size. The large difference between the sedimentation constant of the $\lambda h80c_{1857}t68dlac$ DNA (40S) and of the repressor (7S) makes it possible to follow radioactively-labeled repressor which is bound to operator DNA through a glycerol gradient. Such studies have yielded the following information[37,49]: the repressor binds to operator with a dissociation constant that is in the range of the expected one, 10^{-11} to 10^{-13} M. The strength of the binding constant is dependent on the concentration of salt; increasing salt concentration weakens the binding. The DNA has to be native; the repressor does not bind to denatured DNA. The interaction is specific, as shown by the fact that the repressor does not bind to $\lambda h80$ DNA. Inducer (IPTG) is able to prohibit the binding. This effect is specific; the anti-inducer ONPF, for example, does not lead to a weakening of the binding.

It has been verified *in vitro* that the binding of repressor to o^c DNA is weaker than that to wild-type DNA. Two o^c's have been used; their behavior was in qualitative agreement with expectations: the stronger the o^c character, the weaker the binding[37,38].

3.5. Physical Consequences of the Tight Binding of Repressor to Operator

The dissociation constant of the repressor-operator complex (K_o) is also defined as the ratio of the backward (k_b) to the forward (k_a) rate constants.

$$K_o = \frac{k_b}{k_a}$$

The repressor has to diffuse to the operator. With the given volume of the cell (10^{-12} cm^3), only seconds are needed until the repressor hits its operator. The conformational changes in the repressor and in the operator may have to occur before the complex is formed. The conformational changes might be fast. The forward rate has been determined to be as high as 7×10^9 mole^{-1} sec^{-1}[50]. This is at least one order of magnitude higher than one would expect. A possible explanation might be one-dimensional diffusion; that is, repressor that hits the DNA not too far from the operator is able to slide along the DNA very rapidly until it hits the operator.

The decay rate of the repressor-operator complex[50] has also been measured: it is as slow as 5×10^{-4} sec^{-1}. The dissociation of half of this complex takes half an hour or so. However, *in vivo* the actual induction process only takes a few seconds[51]. (The two reports which seem to give opposite evidence are probably wrong[52,53].) We are thus left with the fact that *in vivo* in the presence of IPTG, repressor falls off the operator very rapidly. The existence of a ternary complex between operator, repressor and IPTG would solve this problem. The strength of the repressor-operator interaction could drop appreciably and thereby lead to fast dissociation *in vitro* and induction *in vivo*. Experiments which prove this have been done *in vitro*, using the filter binding technique[50]. In the presence of IPTG, the decay rate of the repressor-operator complex is so fast that it cannot be measured[54]. The existence of the ternary IPTG-repressor-operator complex is not so astonishing as it might at first seem. It has been known for a long time that not all inducers give maximal levels of induction at the highest inducer levels. With one inducer, methyl-1-thio-β-D-galactopyranoside (TMG), a close analog of IPTG, the maximal level of induction is lower by 20% than with IPTG[55]. This can be easily explained by a strong binding of the TMG repressor complex to the operator; at the highest TMG concentration, 20% of the operator is inactive because it forms the ternary complex. In the same kinetic study[54] it was shown that the ternary repressor-ONPF-operator complex was more stable than the binary repressor-operator complex.

3.6. The Size of the Operator

One can try to deduce the size of the operator by simple reasoning. If the operator has no secondary structure, and if the repressor has to bind only to the operator site and to no other site of the DNA in *E.coli*, it has to be at least twelve base pairs long. If:

A = the number of base pairs in an *E.coli* chromosome
B = the number of different bases
n = the number of base pairs whose sequence occurs only once on the chromosome,

then we have:

$$A = B^n$$
$$3.5 \times 10^6 = 4^n$$
$$= 11 \text{ to } 12$$

There are some hidden assumptions in this calculation: the DNA must be a random polymer, or more specifically, operators in general may not share common se-

quences. The close linkage between the operator and the promoter could speak against such an assumption. If the sharing of common structures in operators is maximal, the number of base pairs to which the repressor actually binds specifically could be appreciably less. Repeating structures[50] which accommodate all subunits and secondary structure in the operator[56] have been discussed, yet there is no *a priori* reason to invoke their existence. Inspections of the space model of DNA suggest that a protein can "see" the base pairs in the large groove. One turn in the helix takes ten base pairs. The physical dimension of 12 base pairs in this arrangement is not too large to be touched by one subunit of the repressor. If every base pair contributes one to two kilocalories to the binding energy, the binding of the repressor to the total structure can become as tight as observed.

Unfortunately, purely genetic measurements do not help in this discussion. The length of the operator could be determined by recombination frequencies between o^c mutants[57], or from the mutation rate of o^c mutants[58]. Recombination frequencies between different o^c mutants have been measured; they give the rather large number of 200 base pairs[57]. They suffer, as do all recombination data for closely-linked markers, from influences from other effects which obscure the actual marker distance. The measurement of frequencies of o^c mutations *versus* i^- mutations has also been attempted[58]. The rather high mutation rate observed for o^c mutants seems to indicate at first glance that the structure is large. It should however be recalled that mutational "hot spots" might completely obscure the data.

Attempts to determine the size of the operator directly by isolating its physical structure are in progress. Operator-containing pieces which contain only 1/20th of the DNA of the λh80dlac phage have been purified[59]; they are 2500 base pairs long and, consequently, substantially larger than the operator itself. Recently, the isolation of a piece of operator DNA 20–23 base pairs long has been reported[60]. ^{32}P labeled $\lambda C_{I857}S7$ plac DNA has been digested with DNAse in the presence of repressor and the shielded pieces have been isolated on nitrocellulose filters.

3.7. Repression *in vitro*

Repression might be tested in two different ways *in vitro*. One might try to measure the repression of an isolated transcription system, or the repression in a protein-synthesizing system. Both have been tried. λh80dlac DNA can be transcribed with RNA polymerase *in vitro*. Lac messenger can be differentiated from the other RNA through a special hybridization test; thus repression can be tested. No repression has been found in a system consisting exclusively of DNA, RNA polymerase, and repressor. It seems that additional factors are necessary. Recently, success has been claimed by the addition of crude ribosomes[61]. The *in vitro* synthesis and repression of β-galactosidase has been claimed several times[62–64]. In the first two cases the results were incorrect; in the third case[64] the results seem to be well substantiated. An interesting fact emerges from these experiments: to function, the system needs a protein (the cap protein) which is common to all catabolite-repressed systems[65,66]. Only the presence of this protein plus cyclic AMP allows effective synthesis of the lac structural proteins.

3.8. Mechanism of Action of the Repressor

How does the repressor act? That is, which process is actually inhibited when repressor is bound to the operator? There are two possible processes with which the repressor might interfere: the start of transcription or RNA chain elongation. If we assume start of transcription, this might be either prohibiting the RNA polymerase from "sitting" on the promoter, or prohibiting the starting reaction of the RNA polymerase.

There is some biological evidence that the repressor might interfere with the start of transcription[67]. A deletion has been isolated which cuts from one of the tryptophan genes into the (transposed) lac promoter. The lac structural genes are now controlled by the tryptophan repressor. The lac operator is far away from the tryp promoter where the transcription of the lac genes now starts. If one turns the tryptophan system on, and if one introduces into this strain an i^+ gene on an episome, the β-galactosidase level in the constitutive tryptophan strain goes down by a factor of 3. This has been taken as evidence that the repressor interferes with RNA chain elongation rather than start of transcription[67]. I would like to interpret the data differently: the three-fold repression of the RNA chain elongation seems to be too weak to be the general mode of action of repressor. If the effect of the repressor is in the steric hindrance of the start of transcription, then o^c mutants might be found which are actually due to insertions between the promoter and the operator. The existence of such o^c mutants will certainly make the mapping of the operator difficult.

4. Evolution of the Control of the Lac System

The lac operon and its regulatory gene are closely-linked. This situation is not the normal one in *E. coli*. In most negative control systems, structural and regulatory genes do not map closely together. What has brought them together in the lac system? To pose the question is to ask for the path of evolution of the lactose system. The product of a regulatory gene must obviously be able to bind a small molecule which is sterically related to at least one of the substrates or products of the enzyme the synthesis of which is to be controlled. It is possible, but not necessary, that the regulatory gene might have arisen by duplication of one of the structural genes to be controlled. That is, the i gene might be related in its structure to parts of the z y a genes. What the "repressor-precursor" needed to learn further was to bind effectively to the chromosome very near the promoter of the structural genes. Duplications seem to map in tandem[68], *i.e.* they lie next to each other. This might be an explanation for the close linkage observed between the

i gene and the structural genes. We can't think of any other reason to bring a regulatory gene, which has arisen elsewhere, into close linkage with the structural genes. We have looked for similarities in the structures of lac repressor and β-galactosidase using immunological methods[46] and have found no cross reaction between repressor and β-galactosidase and their antibodies in an Ouchterlony test. This makes a close structural relationship between the two unlikely.

It is not known during which time span the evolution of the lac genes occurred. In *Shigella* (a closely related bacterium) the y gene is lacking[69]. Has it been lost or has *Shigella* never acquired a transport system for lactose? The i^+z^+ genes alone are not useless: *Shigella* cannot grow on lactose but it can grow on methylgalactoside or galactosidoglycerol, since these are transported by a different transport system. It has been pointed out[12] that lactose occurs only in mammals, and that *E.coli* must be older in origin than the mammals in which it now lives. Galactolipids are extremely frequent in plants; it might be that the lac system has to be traced back to times when galactolipids were the original substrate for *E.coli*. Alternatively the lac system may be of rather recent origin; this could explain the close linkage between structural and regulatory genes: the lac genes have not yet had the time to separate as have the very old regulatory and structural genes which are involved in the production of amino acids.

5. How General is Negative Control of Protein Synthesis?

At the time when *Jacob* and *Monod* proposed their model, it looked as if it were the only one operating in *E.coli*. In the meantime, more systems have been analyzed extensively. In particular, the λ and $i_{434}c_I$ control systems are fully analogous to the lac system: λ and $i_{434}c_I$ product is oligomeric [70] and binds to operator DNA[71,72]. About half of all the systems in *E.coli* seem to follow the Jacob-Monod scheme in every respect but the other half seem to operate differently. Here we have the characteristics of positive control: in the absence of the product of a regulatory gene, none of the products of the structural genes are made. Genetical analysis makes it appear rather unlikely that behind these apparently positive control systems other still unidentified negative control systems are lurking. Yet there is a way in which they might be reduced to negative control systems. Prevention of normal stop might be the basis of these control systems. If this happens to occur at the transcriptional level, then only in the presence of the product of the regulatory gene would transcription proceed to the structural genes. Alternatively, sigma factors[73] which give the RNA polymerase specificity towards promoters may be involved. The biochemical analysis, which alone can prove these mechanisms, has yet to be performed.

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The Mechanism of Contact Elimination, A Contribution to Understanding the Function of Polar Catalysts

By Heinrich Noller, Paulino Andréu, and Manfred Hunger[*]

The current ideas of organic chemists based on the work of Ingold and his school are applied to heterogeneous catalytic eliminations (mostly from haloalkanes and aliphatic alcohols). It is deduced from the activity of the catalysts, the reactivity of the substrates (reactants), and the primary product distribution that these eliminations proceed by a heterolytic mechanism similar to that involved in the liquid phase. The activity of the catalysts (salts and oxides) increases with increasing charge and decreasing radius of the cations and with increasing basicity of the anions. The reactivity of the substrates behaves in much the same manner as in the liquid phase. In contrast with the liquid-phase reaction, the cis-olefins are frequently favored as primary products. The stereospecificity of the reaction is determined from the relative strengths of the interactions between the catalyst cation and the leaving group X^-, and between the catalyst anion and the leaving proton. Only trans elimination has so far been found in the concerted mechanism.

1. Introduction

This article will be concerned exclusively with β-eliminations, mostly from haloalkanes and aliphatic alcohols[1,2]. The reactants in every case will be gaseous (at the reaction temperature), and the catalysts will be solid. The reaction takes place on the surface of the solid.

$$X\text{-}C_{\alpha}\text{-}C_{\beta}\text{-}H \longrightarrow C{=}C + HX$$

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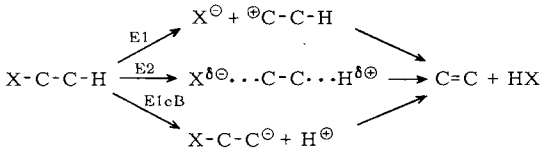
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In some respects, contact elimination (elimination over catalysts) occupies an intermediate position between eliminations in the liquid phase and in the gas phase. Elimination in the liquid phase is generally regarded as a heterolytic process. *Maccoll*[3] also assumes a heterolytic or, to put it more cautiously, "quasi-heterolytic" course for the gas phase reaction (see also ref. [1], p. 182ff). In our opinion, contact elimination also follows a heterolytic mechanism. Experimental evidence in favor of this assumption is the observation that this type of reaction is catalyzed only by polar substances (salts and oxides), and not by metals. The kinetics, the activity of the catalysts, the reactivity of the substrates, and the primary product distribution were studied in order to obtain information about the mechanism. The reactivity includes the kinetic isotope effect, and the primary product distribution the distribution of isotopes in the products.

2. Kinetics

In contact eliminations, as in the liquid phase, it is necessary to differentiate between E1, E2, and E1cB eliminations. These possibilities are shown in Scheme 1.



Scheme 1.

In the E1 mechanism, the reaction begins with the abstraction of X. Since X is generally more electronegative than H, this first step yields a carbonium ion, which has a definite lifetime and loses a proton in the second step. The potential energy profile has two maxima separated by a minimum, which corresponds to the carbonium ion.

The E1cB mechanism (cB = conjugated base) begins with the cleavage of C–H bond. The energy profile again has two maxima; the intervening minimum corresponds to the carbanion.

In the E2 mechanism, which is also described as a concerted or multi-center process, H and X are removed simultaneously. However, the process will be truly synchronous only in exceptional cases, if at all, and the reaction will normally begin with the lengthening of only one bond. Before the rupture of this bond is complete, the other bond begins to break. Thus the rupture of the two bonds has proceeded to different extents in the activated complex[1,2]. The concerted reaction thus covers a broad range of possibilities with tendencies toward E1 or E1cB. The essential feature is that the energy profile has only one maximum.

In the liquid phase, the criterion of an E1 mechanism is taken to be a reaction order of 1 with respect to the reactant, the reaction being independent of the base concentration, while the criterion of the E2 mechanism is a reaction order of 2, *i.e.* the reaction is first order with respect to the reactant and the base. Since the function of the base is taken over in the contact reaction by the anions of the catalyst, the concentration of which does not change, both the carbonium ion mechanism (E1) and the concerted mechanism (E2) should give a reaction order of 1. With certain reservations, this is in fact the result obtained in the investigations so far.

For the catalytic elimination of HCl from ethyl chloride, *Cremer* and *Baldt*[4] found a reaction order of 1 with respect to the reactant up to a conversion of about 50%. This was confirmed by *Schwab* and *Noller*[5]. *Noller* and *Wolff*[6] were then able to show that deviations from the first order are due to the influence of the reverse reaction, *i.e.* the addition. The simple equation:

$$R = k_{el} p(C_2H_5Cl) \qquad (1)$$

must therefore be replaced by an equation that takes the reverse reaction into account:

$$R = k_{el}\, p(C_2H_5Cl) - k_{ad}\, p(C_2H_4) p(HCl) \qquad (2)$$

(R = reaction rate; k = rate constant; el = elimination; ad = addition; p = pressure). This equation was also used by *Simkovich* and *Wagner*[7].

The importance of the second term depends on the position of the equilibrium. *Heinzelmann*[8] used conditions of practically complete elimination (ethyl chloride at about 300 °C, pressures below 50 torr, flow apparatus, carrier gas He, catalysts $MgSO_4$ and Al_2O_3). Under these conditions, eq. (1) is satisfied up to conversions of more than 80%. However, the constant k_{el} decreases with increasing initial pressure. At a given (initial) pressure, the elimination itself (*i.e.* without interference from the addition) is of 1st order (unimolecular reaction).

Unlike in the liquid phase reaction, it is difficult to draw any further conclusions from the kinetics.

3. Activity of the Catalysts

There is no generally accepted measure of catalyst activity. We use the reaction rate *(R)* in some cases and the activation energy *(AE)*[*] in others.

3.1. Effect of the Cations

A preliminary survey is provided by Table 1. The alkaline earth metal ions are more active than the alkali metal ions. This may be thought of as resulting from the stronger electric field of the bivalent cations or from their more strongly electrophilic properties, which amounts to the same thing here. Within each of the two groups, the activity decreases from top to bottom of the periodic table, *i.e.* with increasing radius, which again corresponds to the strength of the electric field (the electrophilic properties).

The result is also influenced by the anion. *Schwab* and *Karatzas*[13] found that with C_2H_5Cl as the reactant,

[*] *I.e.* the Arrhenius activation energy, which we regard as equivalent to the Eyring activation enthalpy (cf. [12]).

Table 1. Activities (activation energies, *AE*) of alkali metal and alkaline earth metal chlorides and sulfates.

Reactant	Catalyst	*AE* (kcal/mole)	Temp. (°C)	Measuring technique	Ref.
2-Chloro-propane	LiCl	20	242 – 271	flowing	[9]
	NaCl	25	362 – 393		
	KCl	46	295 – 315		
2-Chloro-propane	$CaCl_2$	18	116 – 189	static	[6]
	$SrCl_2$	20	128 – 171		
	$BaCl_2$	28	82 – 142		
	$CaSO_4$	17	72 – 132		
2-Chloro-butane	$MgSO_4$	13	150 – 300	pulsed	[10, 11]
	$CaSO_4$	16	180 – 320		
	$BaSO_4$	22	250 – 400		

$Ba[MnCl_4]$ with its bivalent anion gave a lower activation energy (13 kcal/mole) than $BaCl_2$ (21 kcal/mole) or $MnCl_2$ (28 kcal/mole) (temperature range 330–380 °C). (For the effect of the anions, see Section 3.3.)

Table 2. Activity of the cations in sulfate catalysts: order of activities, activation energies *(AE)*, temperature ranges, and cation radii [14] (reactant: 2-bromobutane; pulse technique [11]).

Activities [a]	Mg^{2+} >	Ba^{2+} >	Be^{2+} >	Al^{3+} >	Li^+ >	K^+
Radius of cation (Å)	0.65	1.35	0.31	0.50	0.60	1.33
AE (kcal/mole)	30	16	24	5	26	15
Temp. (°C)	90-120	100-160	120-220	150-250	200-330	170-380

[a] The reaction rate was used as a measure of the activity

A fundamental difficulty in the comparison of activities is that more than one of the properties (nature, size, and charge of the ions and crystal structure) change when the catalyst is changed. If we consider the values for catalysts with cations of roughly equal size in Table 2[14], we find that the order of the activities of the cations is similar for 2-bromobutane, 2-chlorobutane, 1-chlorobutane, and 1-bromobutane[14]. The monovalent cations are again less active than those with higher valencies. Mg^{2+} is the most active, whereas Al^{3+} should be more active if the activity was determined purely by the size and the charge. Another factor presumably involved is lack of accessibility, *i.e.* shielding *e.g.* by anions, which is relatively pronounced in the case of small cations (Be^{2+}) and with an unfavorable ratio of the number of cations to the number of anions (Al^{3+}). $AlPO_4$, which has a more favorable cation to anion ratio, is in fact more activity than $Al_2(SO_4)_3$[15]. The reaction rate was used here as a measure of the activity.

The effect of the cations is also clear in the case of zeolite catalysts. As was found by *Venuto, Givens, Hamilton,* and *Landis*[16] the Linde molecular sieves X and Y[16a] in the lanthanide, Na, Ni, H, and Ag forms are more active for the elimination of HCl from ethyl chloride than the cracking catalyst 46 AI (silica alumina) of the Socony Mobil Oil Company (activity measure: reaction rate at 260 °C).

Similar patterns are found in the dehydration of alcohols. *Galitsch et al.*[17] obtained the following sequence of activities (reaction rates) with 1-butanol on zeolites (molecular sieves): LiNaX > NaX > KNaX > RbNaX. *Scharf et al.*[18] found the sequence HNaY > ZnNaY > MgNaY > ZnNaX > MgNaX > NaY > NaX with 1-pentanol (measure of activity: reaction rate in the temperature range 170 to 400 °C). The activity of the cations is again determined largely by their charge (valency) and size.

3.2. Relationship between Catalytic Elimination and Cracking

This relationship is revealed in the work of *Rabo et al.*[19], who like the present authors, regard the electric field (which depends on size and charge) as the factor that decides the catalytic action of the ions. The order of the activities of various forms of Linde molecular sieves X and Y[16a] for the cracking of hexane is as follows: NaX ≈ NaY ≈ silica alumina (cracking catalyst) < BaY < MgX < SrY < CaY < MgY. The Y series is more active than the X series, showing that the "anion" has some influence. A corresponding activity sequence was found for the cracking of cumene (isopropylbenzene): NaY < BaY < SrY < CaY ≈ MgY ≈ BeY. LaY has a much higher cracking activity than NaY (reactant: butane, measure of activity: reaction rate in the temperature range between 360 and 500 °C).

3.3. Effect of the Anions

The effect of the anions (Table 3) is not so clear as that of the cations. There seems to be a certain parallelism with the basicity. The important quantity is presumably not so much the basicity as the rate of combination of the base and the proton, which is sometimes referred to as the nucleophilicity[2].

Table 3. Activity of the anions of lithium salts [20]: order of activities, activation energies *(AE)*, and temperature ranges (reactant: 2-chlorobutane; pulse technique [11]). The reaction rate was used as a measure of the activity.

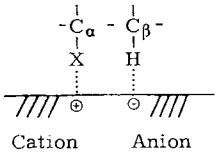
Activities	PO_4^{3-} >	SO_4^{2-} >	F^- >	CO_3^{2-} >	Br^- >	Cl^-
AE (kcal/mole)	25	16	18	25	26	25
Temp. (°C)	150-260	170-375	160-440	190-400	200-400	290-420

3.4. Views on the Catalyst Action

The division of the catalyst action into a cationic and an anionic component corresponds to the distinction usually made in liquid-phase reactions between cationoid (Lewis acid, electrophilic) and anionoid (basic, nucleophilic) components of the reaction medium. The fact that the eliminations in question are catalyzed only by polar substances, and not by metals, shows that this dual action of the catalyst is important[21].

The activities found for the cations and anions indicate that the cation removes the halogen from the alkyl halide in the form of a halide ion, whereas the anion takes up a proton from C_β. As was suggested by *Schwab* and *Karatzas*[13], the interaction between the catalyst and the reactant can therefore be formulated as shown in *(1)*, steric aspects being disregarded.

The action of the cation frequently appears to be more decisive than that of the anion, *i.e.* the attack of the electrophilic centers of the catalyst (cations) on the C–X bond seems to be more effective than the attack of the nucleophilic (basic) centers (anions) on the C–H bond.



(1)

Since, with X=halogen, the rupture of the C–X bond is easier than that of the C–H bond, the process seems to follow the obvious principle that the reaction begins with the attack of the catalyst on the weakest part of the molecule.

For the application of the semiconductor theory of catalysis to elimination reactions, see [7,22].

4. Reactivity

4.1. Ease of Removal of the Group X

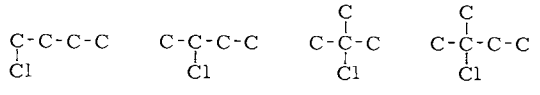
For 1-X-butane and 2-X-butane over the sulfate catalysts[14] of Table 2 and over calcium sulfate and calcium phosphate[23], the following sequence was found for the ease of removal.

X	Br ≈ Cl > OH > NH_2 > C_6H_5				
Homolytic dissociation energy[24] of the C–X bond in C_2H_5–X (kcal/mole)	65	82	93	78	94

Thus the ease of removal (measured by the reaction rate in the temperature range between 200 and 350 °C) does not vary parallel with the homolytic dissociation energy.

4.2. Primary, Secondary, and Tertiary Carbon Atoms

The ease of removal of a substituent X also depends on whether it is attached to a primary, a secondary, or a tertiary carbon atom. As in the liquid phase, the ease of removal increases in the above order. The following activation energies (in kcal/mole) were found on $CaCl_2$ between 100 and 350 °C[25]:



The reactivity series for cracking on silica alumina is[26]: *tert*-butylbenzene > *sec*-butylbenzene > cumene (isopropylbenzene) > *n*-butylbenzene. The similarity of elimination and cracking is again clear. This is also true of the cracking of aliphatic compounds. The relative reactivities of primary, secondary, and tertiary carbon atoms in hexane were found to be related as 1 : 2 : 20[27]. *Dohse* found this reactivity sequence as early as 1931[28] for the dehydration of alcohols on bauxite (Table 5).

4.3. Effect of Substituents

The following activation energies *(AE)* were obtained for a series of 1-chloro-*n*-alkanes on $BaSO_4$ between 160 and 400 °C[29]:

Number of C atoms	2	3	4	5	6	7
AE (kcal/mole)	17	12	19	15	10	10

The activation energy does not show a monotonic variation with the chain length (β-substitution by alkyl groups). The result is presumably due to a complex interplay of neighboring-group and inductive effects. The inductive effect of the alkyl group itself acts in opposite directions. On the one hand, it favors removal of X^-, while on the other it hinders the removal of the proton (C_β also carries a greater negative charge, and so holds the proton more strongly). The latter effect is more pronounced in the E2 mechanism than in the E1. According to *Bunnett*[2], β-alkyl groups displace the mechanism toward E1 (Table 11).

The effects of electronegative substituents in the β position (which, according to *Bunnett*[2], displace the reaction course toward E1cB) are shown in Table 4. There is a clear difference in behavior here between the catalysts $MgSO_4$ and K_2CO_3. $MgSO_4$ is an E1 catalyst, while K_2CO_3 is an E2 catalyst[*] (for further details see Section 5.4). In the E1 mechanism, the β-chlorine atom hinders the (rate-determining) removal of the chloride ion and the formation of the carbonium ion; this hindrance also occurs in the E2 mechanism, but is more than compensated by the greater ease of removal of the proton and the conjugation of the p electrons of the remaining chlorine with the double bond being formed.

A phenyl group in the β position acts in the same manner as an electronegative substituent (see Table 7).

Table 4. Activation energies [30] (in kcal/mole) determined between 160 and 350 °C for ethane with electronegative substituents (chlorine).

Reactant		Cl-C_α-C	Cl-C_α-C_β-Cl	Cl-C_α(Cl)-C	Cl-C_α-C_β-Cl	Cl-C_α(Cl)-C
Catalyst (E1)	$MgSO_4$	23	very high	33	very high	21
Catalyst (E2)	K_2CO_3	24	16	24	14	33

α-Substitution by a methyl group considerably increases the reactivity (Table 5). The effect is similar in its magnitude to that found by *Maccoll*[1,3] and earlier by *Barton*[31] for the homogeneous reaction in the gas phase. In both the homogeneous and the contact reactions, the activation energies vary in the same manner as the energies of the heterolytic rather than of the homolytic dissociation. *Maccoll* concluded that the gas phase reaction is a (quasi)heterolytic process, like the E1 process in the liquid phase. We believe that the same is true of

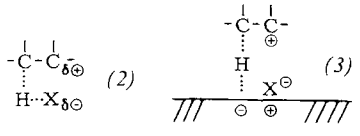
[*] Statements of this type are always intended to be taken relatively, since the mechanism also depends on the reactant. In the present case, therefore, we mean that K_2CO_3 favors the E2 mechanism more than $MgSO_4$. If, on the other hand, $MgSO_4$ gave an E2 mechanism (a situation that did not occur with our substrates), K_2CO_3 would give a shift toward E1cB (cf. [2]).

the contact reaction. The activation energies for the dehydration of alcohols on bauxite vary in the same manner[28] (Table 5).

Table 5. α-Substitution by electron-donating substituents (methyl), activation energies *(AE)* for the contact reaction on LiCl, and the homogeneous reaction; also energies of the homolytic and heterolytic dissociation *(D)* (all in kcal/mole). For comparison: Activation energies of the dehydration of alcohols on bauxite (values based on *AE* measured between 150 and 400°C).

	X-C-C	C-C-C (X)	C-C(C)-C (X)
Catalyst LiCl[9] (X=Cl) *AE*	25	20	16
Homogeneous reaction[1, 3] (X=Cl) *AE*	60	51	41
D (R-Cl)	81	82	78
D ($R^{\oplus}$-$Cl^{\ominus}$)	193	166	150
Catalyst Bauxite[28] (X=OH) *AE*	31	25.5	20

Banthorpe[1] thought it probable that the addition in the gas phase (homogeneous reaction) involved the transition state *(2)*. On the basis of the principle of microscopic reversibility, he also suggested this same transition state for the elimination in the gas phase[1].



A similar transition state *(3)* seems probable for the contact reaction in the E1 case. The activated complex *(3)* evidently requires less energy for its formation than *(2)*, and this is the basis of the catalyst action.

The action of the catalyst is comparable to that of a solvating solvent. As was shown by *Gutmann*[32], the ability of such a solvent to heterolyze covalent bonds and to stabilize the resulting ions is a phenomenon of coordination chemistry. Similarly, the polar catalyst causes the heterolysis of the bonds that have to be broken in the reaction by stabilizing the ionic structures that occur in the transition state through coordination. The effect of the catalyst, which consists in a decrease in the activation energy, may therefore also be regarded as a phenomenon of coordination chemistry. Differences are, however, seen in the fact that no "all-round solvation" occurs in catalysis and that the transition states are unstable structures along the reaction coordinate.

Electronegative substituents in the α position hinder the E1 elimination (catalysis by $MgSO_4$, Table 4) since the second chlorine atom makes it more difficult for the first to take the electrons with it. The E2 elimination, on the other hand, is not affected (catalysis by K_2CO_3, Table 4). Though the removal of the electrons with the first chlorine atom is still made more difficult, this is offset by the conjugation of the remaining chlorine with the double bond being formed.

A second additional chlorine atom (1,1,1-trichloroethane, Table 4) probably causes a transition toward E2 over $MgSO_4$ (since the removal of the chloride is now even more difficult, whereas that of the proton is easier, so that the rupture of both bonds is roughly equally difficult), and the activation energy of the E2 elimination may be less than that of the E1 process because of the possibilities of conjugation. On K_2CO_3, on the other hand, there is a further increase in the difficulty of removal of the chloride, which evidently cannot be offset by the conjugation of the resulting double bond with two chlorine atoms.

Mochida[33] found the reactivity sequence given in Table 6 on several catalysts. This sequence is similar to that on $MgSO_4$ (Table 4). The same sequence is given by *Venuto, Givens, Hamilton,* and *Landis*[16] for a lanthanide-loaded molecular sieve (REX in Table 6).

Table 6. Effects of electronegative substituents in the α and β positions.

Catalyst	Order of reactivities [a]	Ref.
SA-1 [b], A-B-1 [c], Mg-10X [d]	Cl_3C-C > Cl_2C-C > Cl_2C-CCl_3 (→ ClC=CCl) > Cl_2C-CCl_2 > ClC-CCl > Cl_2C-CCl (→ Cl_2C=C)	[33]
Cr_2O_3	Cl_3C-C > Cl_2C-C > Cl_2C-CCl_2 > Cl_2C-CCl (→ClC=CCl)>ClC-CCl > Cl_2C-CCl (→ Cl_2C=C)	[33]
REX [e]	Cl_3C-C > Cl_2C-C > ClC-CCl	[16]

[a] The reaction rate at 300°C was used as a measure.
[b] Silica alumina (13% Al_2O_3).
[c] Alumina boria (10% B_2O_3).
[d] Linde molecular sieve 10X, Mg form.
[e] Linde molecular sieve 13X, loaded with a mixture of lanthanides.

Table 7. Effects of methyl and phenyl substitution. Expected sequence of activation energies *(AE)* and experimental activation energies (in kcal/mole) measured between 100 and 450°C.

Expected order of *AE* for E1	Cl-C(C$_6$H$_5$)-C	<	C-C(Cl)-C	<	Cl-C-C-C	<	Cl-C-C-C_6H_5	<	Cl-C-C
Found *AE* on $MgSO_4$	–		6		9		11		19
Found *AE* on $BaSO_4$	–		8		10		15		–
Expected order of *AE* for E2	Cl-C(C$_6$H$_5$)-C	≈	Cl-C-C-C_6H_5	<	C-C(Cl)-C	<	Cl-C-C-C	<	Cl-C-C
Found *AE* on K_2CO_3	–		17		24		38		–
Found *AE* on K_3PO_4	–		9		13		18		–

If ethyl chloride is substituted in the α and β positions with methyl or phenyl groups[34], the sequences indicated in Table 7 are to be expected for the activation energies,

depending on whether the process is E1 or E2[34]. Chloroethane reacts so reluctantly that it has only been studied in one case. 1-Chloro-1-phenylethane, on the other hand, reacts so readily that the activation energy could not be determined. The (E1-like) homogeneous reaction is so strongly supported by the α-phenyl group that it is complete even at about 100 °C.

The sequences found on $MgSO_4$ and $BaSO_4$ (E1 catalysts) agree with those expected. On K_2CO_3 and K_3PO_4 (E2 catalysts), though 1-chloro-2-phenylethane has the lowest activation energy, as expected, the difference between 1-chloropropane and 2-chloropropane should be smaller. The great difference found presumably means that the dissociation of the C–Cl bond has progressed much farther in the transition state than that of the C–H bond, *i.e.* that the reaction is a concerted process with a tendency toward E1[1,2].

4.4. Kinetic Isotope Effect

The reaction rates were determined for the following series on magnesium sulfate and magnesium phosphate: CH_3-CHCl-CH_3 (D_0), CH_3-CDCl-CH_3 (D_1), CD_3-CHCl-CD_3 (D_6), CD_3-CDCl-CD_3 (D_7). The rate of D_0 is practically equal to that of D_1, and that of D_6 is equal to that of D_7. The ratio $k(D_{0,1})/k(D_{6,7})$ of the rate constants is 1.7 on magnesium phosphate at 320 °C[35] and 3 on magnesium sulfate at 160 °C[36].

Isotope effects of this magnitude are compatible with an E1 mechanism[1] such as is to be expected for both catalysts (see Section 5.4).

With the C_β-deuterated alcohols isobutanol $(CH_3)_2CD$-CH_2OH, *sec*-butanol, C_2D_5-CH(OH)-CH_3, and *tert*-butanol $(CD_3)_3COH$ on Al_2O_3, *Knözinger* and *Schegli-la*[37] found an isotope effect (k_H/k_D) of between 3.95 (*sec*-BuOH at 120 °C) and 1.7 (*iso*-BuOH at 200 °C). They deduce an E2-like dehydration mechanism, which tends toward E1 with rising temperature.

No secondary isotope effect was observed. On introduction of a D atom on C_α, though the conversion of the deuterated reactant is always slightly less than that of the undeuterated material, the differences are less than 10% (CH_3-CDCl-CH_3 on $MgSO_4$, $BaSO_4$[10]; CH_3-CDCl-C_2H_5 on $CaCl_2$[38]; CH_3-CDOH-C_2H_5 on $CaSO_4$[39]).

5. The Primary Product Distribution

The determination of the primary products is a particularly important means of obtaining an insight into the mechanism of a reaction. Whereas the equilibrium distribution is determined by the difference in the free energies (enthalpies) (thermodynamic control), the primary product distribution depends on the difference in the free activation energies (enthalpies) (kinetic control). The primary product distribution should therefore generally be different from the equilibrium distribution, the only exceptions being the extremly rare cases in which the two energy differences are equal. Kinetic control should therefore always be found. If, however, it is thought that "thermodynamic control" has been detected, this may be taken either as a sign of secondary reactions that lead to an equilibrium or as an indication that the reaction temperature is too high to allow the difference in the two energy differences to become effective.

5.1. Orientation

In contact eliminations from compounds that can form several olefins, Saytzeff orientation has nearly always been found so far. Thus, the olefin with the greater number of alkyl groups predominates. This is true not only with 2-halobutanes[23,25,38–41], 2-halopentanes[42], and *tert*-amyl chloride[42] on various salt and oxide catalysts, but also for 2-butanol[37,39,43,43a]. The Saytzeff orientation is also favored with 2-aminobutane[43b] and 2-phenylbutane[26] on silica alumina. It is generally accepted[1,2] that the Saytzeff orientation is characteristic of E1 and possibly E2, but less so for E1cB.

It is interesting to note that the Hofmann orientation is found in the dehydration of alcohols on thorium oxide. 2-Butanol thus gives mainly 1-butene[44], and even 3-methyl-2-pentanol gives about 80% of 3-methyl-1-pentene at 360 °C[45].

5.2. Wagner-Meerwein Rearrangement

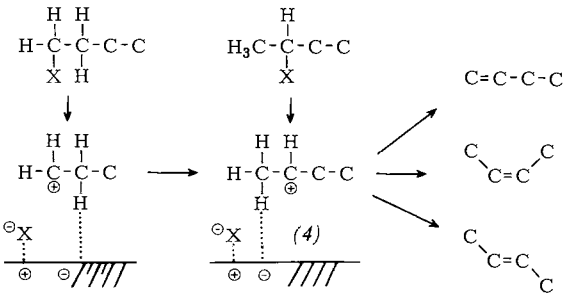
Though 1-X-butane always reacts less readily than 2-X-butane in contact eliminations, the products are the same and the product distributions are frequently similar, particularly with X=Cl, Br. 2-Butene usually predominates[23,25,40–42]. Some examples are shown in Table 8. This presumably means that both reactants form the same 2-butyl cation *(4)*; in the case of 1-X-butane, this cation is formed by Wagner-Meerwein rearrangement of the initially formed 1-butyl cation.

Table 8. Similarity of the product distribution with 1-chlorobutane and 2-chlorobutane as reactants, and examples of preferred formation of *cis* olefin [41].

Catalyst	Temp. (°C)	Reactant	Conversion (%) [a]	1-Butene (%) [b]	*trans*-2-Butene (%) [b]	*cis*-2-Butene (%) [b]
$MgSO_4$	240	1-Cl-Butane	80	10	60	30
$MgSO_4$	240	2-Cl-Butane	100	13	59	28
$BaSO_4$	245	1-Cl-Butane	70	21	36	43
$BaSO_4$	130	2-Cl-Butane	34	7	32	61
$BaSO_4$	180	2-Cl-Butane	97	9	46	45
Li_2SO_4	390	1-Cl-Butane	10	100	–	–
Li_2SO_4	270	2-Cl-Butane	10	15	27	58
Li_2SO_4	330	2-Cl-Butane	39	19	32	49
Li_2SO_4	390	2-Cl-Butane	100	22	40	38

[a] Based on the reactant as 100%.
[b] Based on the sum of the butenes as 100%.

This similarity of the product distribution is further evidence in favor of an E1 mechanism with a carbonium ion as the intermediate. In addition to hydride shifts,



rearrangements of the carbon skeleton are also observed. Neopentyl bromide on Al_2O_3, even around 100 °C, gives 2-methyl-2-butene (principal product) and 2-methyl-1-butene[42]. The only catalysts that allow the preferential formation of 1-butene from 1-halobutanes are lithium salts[20,41,46] (Table 8). If the halogen is replaced by a substituent that is more difficult to remove, displacement of the mechanism toward E2 is to be expected. It is in fact found that 1-butyl acetate on $MgSO_4$, which is a pronounced E1 catalyst for haloalkanes, gives between 50 and 60% of 1-butene. $BaSO_4$, which is also an E1 catalyst for haloalkanes, though less so than $MgSO_4$, leads to the exclusive formation of 1-butene[47].

5.3. Preferential *cis*-Olefin Formation

An interesting characteristic of contact eliminations is that the (thermodynamically less stable) *cis*-olefin is frequently favored over the *trans*-olefin in the primary products (Table 8). The *cis*-olefin is nearly always formed in a quantity greater than that corresponding to the equilibrium[20,23,25,38–41]. *Knözinger* and *Bühl* recently found the extremely high *cis/trans* ratio of 10:1 with 2-butanol on Al_2O_3[43].

This characteristic is particularly pronounced on lithium salts[20], while it is weaker or even absent on very active catalysts (particularly selective catalysts such as lithium salts are often only moderately active). The distribution approaches equilibrium with rising temperature.

5.4. Stereoselectivity and Stereospecificity

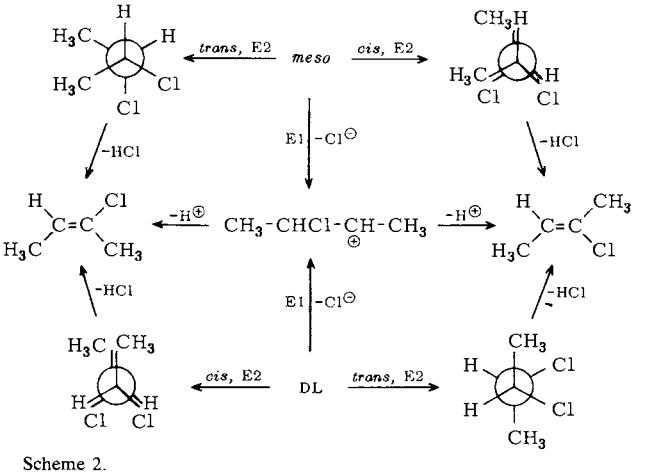
We use the term stereoselectivity with respect to the catalyst, and the term stereospecificity with respect to the reaction in general.

One method of obtaining information about stereoselectivity and stereospecificity is the use of cyclic compounds. In the investigation of the dehydration of menthol or neomenthol on Al_2O_3, *Pines* and *Pillai* came to the surprising conclusion that this reaction must be a *trans*-elimination[48]. A similar result was obtained by *Blanc* and *Pines*[49] with other alkyl- and phenyl-substituted cyclohexanols, again on Al_2O_3. This observation of *trans*-elimination was recently confirmed by *Blanchard* and *Canesson*, who investigated the dehydration of 2-methyl-1-cyclohexanol on thorium oxide[50]. The present authors obtained a similar result in the contact elimination of HCl from menthyl chloride and neomenthyl chloride on $CaCl_2$ and other salt catalysts[51].

Another possibility is the use of substances in which the starting positions of H and X are fixed from the outset with respect to each other, *e.g. cis*- and *trans*-chlorostilbenes, both of which give tolan. Investigations using numerous salt and oxide catalysts have shown[40,52] that both isomers react, the *cis*-isomer usually more readily than the *trans*-isomer. However, this must not be taken directly as an indication that the *cis*-elimination is preferred, since *cis*-chlorostilbene has undoubtedly a higher energy than *trans*-chlorostilbene (the difference in the case of *cis*-stilbene and *trans*-stilbene is 9.5 kcal/mole[53]). *cis*-Chlorostilbene is thus presumably closer in energy to the activated complex than *trans*-chlorostilbene, though the two complexes need not be identical. The results show that both elimination mechanisms are fundamentally possible.

The best method for the recognition of stereoselectivity and stereospecificity is probably use of compounds with asymmetric α- and β-C atoms. We have made considerable use of 2,3-dichlorobutane[54,55,55a], as well as of 2,3-dibromobutane[56] and 1,2-dichloro-1,2-diphenylethane[57].

Scheme 2 shows what one should expect from the various mechanisms in the case of 2,3-dichlorobutanes. The decisive information is provided by the ratio of *cis*- to *trans*-2-chloro-2-butene and from the difference in this ratio according to whether the *meso* or DL form of the reactant is used.



Scheme 2.

In the case of a concerted *cis*-elimination (E2), the *meso*-form gives the *trans*-olefin, while the DL-form gives the *cis*-olefin; the result is reversed in a concerted *trans*-elimination. If the mechanism is E1, both forms give the same carbonium ion, and this logically gives the same *cis/trans* ratio of the olefins.

Table 9 shows a list of catalysts in order of decreasing stereoselectivity. The stereoselectivity was measured by the difference in the ratios of *cis*- to *trans*-2-chloro-2-butene obtained from the *meso*- and DL-forms. It increases with decreasing charge and increasing radius of the cation, as well as with increasing basicity of the anion.

This principle is obvious if one bears in mind the adsorption [as in *(1)*, Section 3.4] and interaction between

the reactant and the catalyst that has already been mentioned several times. If the cation-X interaction predominates, X is removed in the first step, corresponding to an E1 mechanism. This is so on most catalysts with polyvalent cations, *i.e.* the more active catalysts. If the cation-X and anion-H interactions are (roughly) equal in strength, an E2 mechanism occurs. With decreasing electrophilicity of the cation and increasing nucleophilicity (basicity) of the anion, therefore, the mechanism is displaced from E1 to E2, and presumably further to E1cB, though this seems to be more difficult. Strengthening of the C–X bond and weakening of the C–H bond should have the same effect.

It is surprising to note that in the E2 process, the *trans* mechanism is favored in the contact elimination, just as in the liquid-phase reaction. It is not yet certain how the proton, which is probably directed away from the surface of the catalyst in the activated complex, reaches this surface. It must be assumed that it is more mobile than is commonly believed (tunneling?)

Aluminum oxide exhibits partial stereoselectivity in the elimination of HCl[55a]. No other oxides have been tested. The *trans*-mechanism has recently also been confirmed in the dehydration of open-chain compounds. *Hall*[58] found it with [3-D]-DL-*erythro*-2-butanol and [3-D]-DL-*threo*-2-butanol on aluminum oxide. *Narayanan* and *Pillai*[45] obtained a similar result in the dehydration of *threo*-3-methyl-2-pentanol both on aluminum oxide and on thorium oxide.

Table 9. Order of stereoselectivities of some catalysts, indicated by the ratio (*cis*+*trans*=100) of *cis*- to *trans*-2-chloro-2-butene obtained from the *meso*- and the DL-forms of 2,3-dichlorobutane (see Scheme 2). The three groups of catalysts correspond to different investigations.

	KBO_2 ≈ K_2CO_3	> K_3PO_4	> K_2SO_4	> $BaCO_3$	> $Ca(BO_2)_2$	> $Ba_3(PO_4)_2$ >
meso	97/3	92/8	93/7	86/14	87/13	46/54	69/31
DL	9/91	7/93	11/89	11/89	19/81	19/81	25/75
Temp. (°C)	250	250	200	280	250	250	250

	$CaCl_2$	K_2CO_3	> Na_2CO_3	> Li_2CO_3	$CaCl_2$[a]	≈ $Ca_3(PO_4)_2$[a]
meso	17/83	98/2	75/25	10/90	22/78	17/83
DL	17/83	35/65[b]	40/60[b]	10/90[b]	23/77	14/86
Temp. (°C)	200	330	330	350	220	220

[a] Reactant: 2,3-dibromobutane.
[b] The DL-form contained more than 10% of the *meso* form.

The elimination of acetic acid from 1-butyl acetate on $BaSO_4$ and $MgSO_4$ was mentioned in Section 5.2. From Table 9, the elimination from 2,3-dichlorobutane should be expected to follow a mixed mechanism on $BaSO_4$ and a pure E1 mechanism on $MgSO_4$. Since the C–O bond is stronger than the C–Cl bond, the elimination from 1-butyl acetate on $BaSO_4$ proceeds almost completely by the E2 mechanism, as is shown by the absence of 2-butene. The olefin distribution in the elimination on $MgSO_4$, on the other hand, points to a mixed mechanism. An increase in the strength of the C–X bond displaces the mechanism toward E2.

In these studies on stereospecificity, we again find the rule that more active catalysts are less selective.

The selectivity generally decreases with rising temperature, again in agreement with the rule, since the catalyst becomes "more active" with rising temperature, and the mechanism shifts from E2 toward E1.

5.5. Is the Reaction really a β-Elimination?

Eliminations of this type are generally tacitly assumed to be β-eliminations, though this should really be checked. Studies by *Schwab*[59] on the dehydration of CH_3-CD_2OH on various catalysts have shown that in most cases (about 80%) hydrogen from the methyl group is removed together with the OH group, *i.e.* that β-elimination at least predominates. Table 10 shows the results of similar studies on [2-D]-2-chloropropane and on [2-D]-2-butanol.

Table 10. The question of β-elimination (loss of deuterium on complete conversion; pulse technique).

Catalyst	Reactant	D content [a]	Temp. (°C)	Product(s)	D content [a]	Ref.
$CaSO_4$	CH_3-CDCl-CH_3	98	320	Propene	94	[10]
$BaSO_4$	CH_3-CDCl-CH_3	98	400	Propene	95	[10]
$MgSO_4$	CH_3-CDCl-CH_3	97	220	Propene	97	[36]
$CaSO_4$	CH_3-CDOH-C_2H_5	96	430	1-Butene+	96	[39]
				trans-2-Butene+	88	
				cis-2-Butene	80	

[a] The values show the percentage of molecules having the number of D atoms that corresponds to the formula.

About 90% of the deuterium present in the reactant is frequently found in the products. In the case of [2-D]-2-butanol on $CaSO_4$, the loss of D in the three butenes

varies[39]. Thus the formation of 1-butene must have been a pure β-elimination. Though slight α-elimination cannot be ruled out in the case of the 2-butenes, it is equally conceivable and compatible with the other findings that the loss of D is connected with the structure of the intermediate carbonium ion.

The loss of D is also relatively small in the elimination of HCl from CH_3-CDCl-CH_3 on $MgSO_4$, $CaSO_4$, and $BaSO_4$.

The results justify the assumption that β-elimination predominates to a great extent.

6. The Factors that Determine the Mechanism

The mechanisms in most of the cases investigated are E1 and E2. The E1cB mechanism has not so far been detected with absolute certainty, though evidence in this direction has been found[60]. This mechanism should occur in systems with strong anion-H interaction and weak cation-X interaction and/or a strong C–X bond and a weak C–H bond.

Bunnett[2] has described how changes in the reaction system alter the mechanism of the elimination in the liquid phase. However, his discussion was confined to the range of the concerted mechanism. We believe that the argument can be confidently extended into the E1 and E1cB regions.

Table 11 shows a modified form of *Bunnett*'s scheme adapted for the contact reaction. Entries 1–5 and 11 need no comment. The effect of electron-attracting β-substituents under 6 is lacking from *Bunnett*'s scheme. Such a substitution should hinder the removal of X and facilitate that of the proton. However, no definite conclusion can be drawn from the few experimental observations, *e.g.* those in Tables 4 and 6.

Table 11. Influence of various factors on the mechanism of contact elimination. For explanations see text.

No.	Factor	E1	E2	ElcB
1.	α-Aryl group	←	—	—
2.	α-Alkyl group	←	—	—
3.	β-Aryl group	—	—	→
4.	β-Alkyl group	←	—	—
5.	Electron-attracting α-substituent	—	—	→
6.	Electron-attracting β-substituent	—	—	→
7.	More readily removed group X	←	—	—
8.	Facilitation of removal of the proton	—	—	→
9.	Higher cation charge	←	—	—
10.	Greater cation radius	—	—	→
11.	Higher anion basicity	—	—	→
12.	Higher shielding of the cation by the anion	—	—	→
13.	Increase of temperature	←	—	—

The item "more readily removed group X" under 7 refers simply to the energy required for the heterolytic dissociation of the C–X bond. It may be assumed that the energy in the transition state shows a corresponding trend. *Bunnett* had included as a further factor the inductive electron attraction of the leaving group, which displaces the mechanism toward E1cB. We have omitted this factor, since we believe that it is difficult in contact elimination to compare reactants that differ only in this respect and not also in the dissociation energies.

The difficulty of removal of the proton (see under 8) is undoubtedly determined by the factors indicated above, but certainly not all the many variations of molecular structure that can affect the ease of removal of the proton have been covered.

The entries under 9 and 10 are not necessarily valid for transition metals. Little is known at present about how empty d orbitals affect the elimination activity. Moreover, it is assumed that the shielding (masking) of the cations by anions is the same. The cations are often smaller than the anions. Such cations are situated slightly deeper in the surface than the anions (see under 12). The more this is so, the smaller is the action of the cation on the reactant, firstly because of the greater distance and secondly because of the stronger shielding by the electron clouds of the anions.

In the case of entry 13 the only experimental observations made so far show that an increase in temperature displaces E2 toward E1[37,54,55,55a] and we do not believe that it can be inferred that E1cB is displaced toward E2; the arrow has therefore been drawn only from E2 to E1. We are of the opinion that the E2 mechanism is always displaced toward one of the ionic mechanisms (carbonium ion or carbanion) by an increase in temperature, but that the direction of the displacement possibly depends on its character at the lower temperature. If this were the case then we would have a further criterion for deciding whether an E2 mechanism had E1 or E1cB character.

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Arguments Concerning the Orbital Sequence in Borazine[1]

By *Hans Bock* and *Werner Fuss*[*]

MO calculations taking account of all valence electrons[2–5] result in an orbital sequence for borazine that is at variance[6] with its photoelectron spectrum[5]; in particular, the highest occupied molecular orbital is calculated to be a σ type orbital. The following considerations and experimental data favor a different assignment:

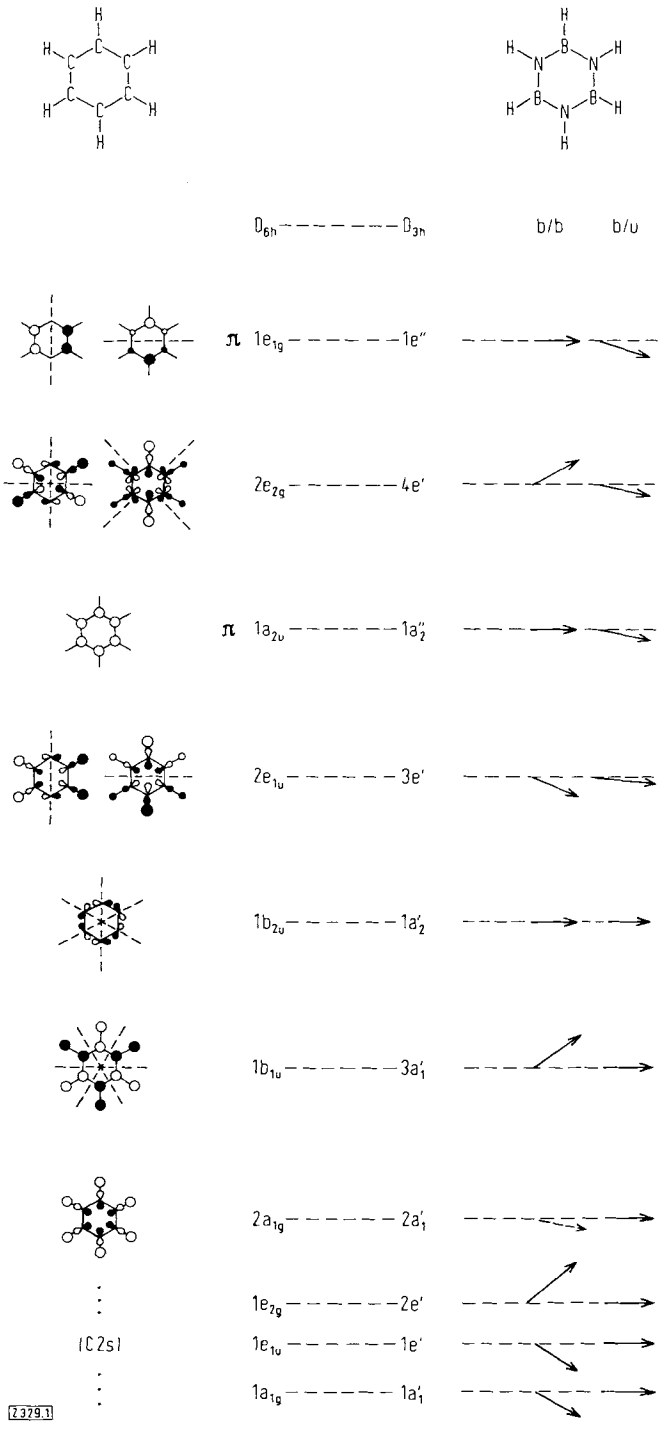


Fig. 1. Qualitative energy level shifts on transition from benzene to borazine.

1) The completely assigned[7] photoelectron spectrum of benzene, a molecule that is isoelectronic with borazine, leads to the sequence of energy levels characterized in Fig. 1 by orbital diagrams and irreducible representations of the corresponding molecular orbitals. On changing from D_{6h} to D_{3h} symmetry, the irreducible representations e_{2g} and e_{1u} coincide in e′ and the irreducible representations b_{1u} and a_{1g} in a_1'[8]. If a perturbation of symmetry D_{3h} is introduced by an alternate raising and lowering of the nuclear charge of the ring atoms then the molecular orbitals of the same irreducible representation will become mixed: The smaller the energy difference between two levels, the greater their "mutual repulsion". The energy level shifts resulting from interactions between occupied molecular orbitals are shown qualitatively in Fig. 1 by the arrows b/b, and additional changes due to the unoccupied molecular orbitals by the arrows b/u. Whether the orbital sequence is altered within this benzene→borazine correlation can be decided experimentally by the assignment of individual bands in the photoelectron spectrum.

2) Six bands (at least) can be distinguished in the PE spectrum of borazine (Fig. 2) up to energies of 21.21 eV[9]. The first band at 10.09 eV is readily assigned to a π ionization on account of its recognizable vibrational fine structure: The progression of 1360± 100 cm^{-1} can only arise from a ring vibration E′ (IR spectrum of borazine: ν_{13} = 1465 or ν_{14} = 1406 cm^{-1}[10]) and, as in the case of benzene, indicates a degenerate level; the progression of 800 ± 40 cm^{-1} corresponds to a ring vibration A_1'

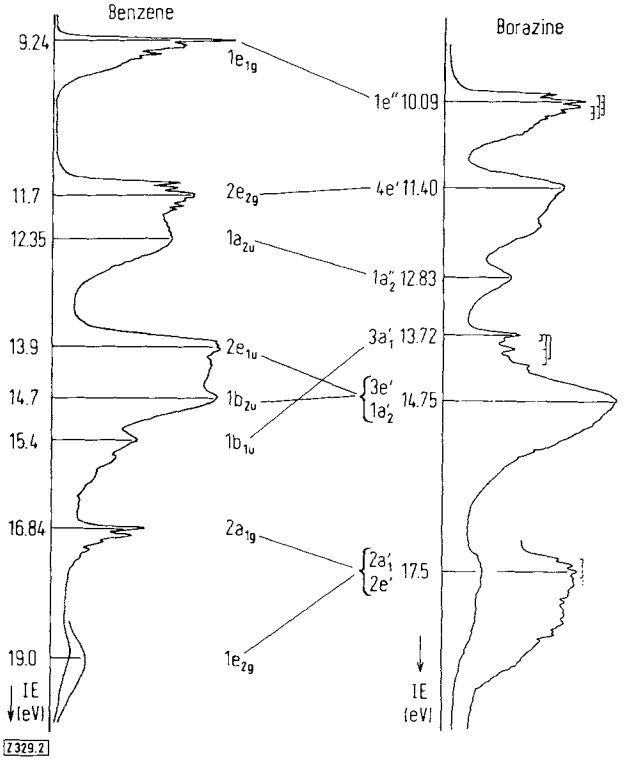


Fig. 2. Correlation of the photoelectron spectra of benzene and borazine [9].

(Raman spectrum of borazine: ν_3 = 944 or ν_4 = 842 cm^{-1}[11]) and is therefore to be assigned to the "ring bonding" π orbital 1e″. For the σ orbital 4e′, which is hardly involved in B/N bonding, there remains only the structureless second band at 11.40 eV. Moreover, the band at 13.72 eV can be assigned to the "strongly B/H bonding" orbital $3a_1'$ on account of its vibrational fine structure: This is confirmed primarily by the appearance

of the B/H stretching vibration 1880 ± 100 cm^{-1} of species A_1' (Raman spectrum of borazine: ν_2 = 2442 cm^{-1}[11]) which, like the C/H stretching vibration of the $1b_{1u}$ band in the photoelectron spectrum of benzene, is drastically lowered by ionization[7]. On the basis of the qualitative orbital correlations (Fig. 1) and the approximate intensity ratios 2:2:0.7:0.7:5:(1), the remaining bands of the borazine photoelectron spectrum are tentatively assigned in the sequence of degenerate and nondegenerate molecular orbitals $e''/e'/a_2''/a_1'/(e' + a_2')/(a_1' + e')$ . . . (Fig. 2).

3) Further arguments supporting the π assignment of the highest occupied borazine molecular orbital arise from the photoelectron spectra of methyl and halogeno derivatives whose first ionization potentials are shown in Fig. 3.

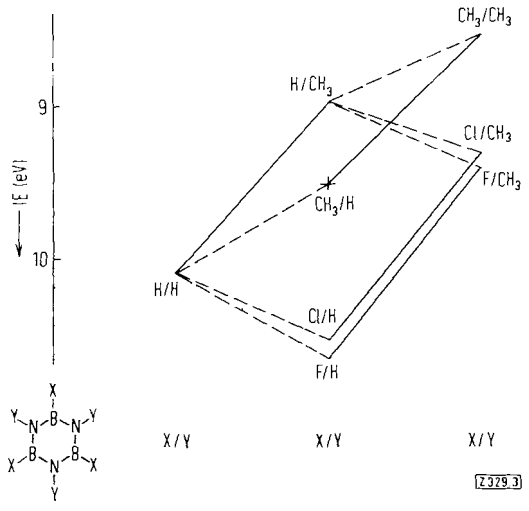


Fig. 3. First ionization potentials of borazine and some of its methyl and halogeno derivatives.

Halogeno substituents X = F,Cl should lower the highest occupied σ level considerably while in a π system the resonance effect of X will oppose the inductive effect[12]: The first band in the photoelectron spectrum of *B*-trifluoroborazine at 10.66 eV and that of *B*-trichloroborazine at 10.55 eV therefore clearly correspond to a π ionization. It also follows from the slight perturbation of the π system that it is the first of the two photoelectron bands of borazine at 10.09 and 11.40 eV (Fig. 2) that has to be assigned to a π orbital.

Methyl groups should have the effect of raising the highest occupied orbital in borazine and its derivatives. According to first order perturbation theory the change in orbital energy

$$\delta\varepsilon_J = \sum_{\varrho} c_{J\varrho}^2 \, \delta\alpha_{\varrho}$$

is given by the perturbation term $\delta\alpha_{\varrho}$ and the square of the orbital coefficient $c_{J\varrho}^2$ at the perturbed center ϱ. Additivity can be expected in the case of several perturbations: As can be seen from Fig. 3, the first ionization potential is altered by the same amount on *N*-methylation (——), independently of the *B*-substituents, and on *B*-methylation or *B*-halogenation (– – –), independently of the *N*-substituents. Such an additivity is not to be expected for σ orbitals, particularly in the case of *B*-halogenoborazines.

Assuming a constant perturbation $\delta\alpha_{\varrho}$ (CH_3), it is also possible to calculate the ratio of the squares of the *B*- and *N*-orbital coefficients: Insertion of the measured mean orbital energy changes $\delta\varepsilon_J(B\text{–}CH_3)$ = 0.55 ± 0.05 eV and $\delta\varepsilon_J(N\text{–}CH_3)$ = 1.1 ± 0.1 eV into the perturbation formula yields $\sum_B c_{JB}^2 : \sum_N c_{JN}^2$ ≈ 1:2 for the highest occupied π orbitals of the borazine derivatives listed in Fig. 3[**].

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[**] *Note added in proof:* In the meantime, *S. D. Peyerimhoff* and *R. J. Buenker* have published an *ab initio* calculation [Theor. Chim. Acta *19*, 1 (1970)] that fully confirms our assignment.

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[9] The PE spectra were recorded with a Perkin-Elmer PS 16 instrument (He I lamp; electrostatic sector field 127°). For higher energies an unavoidable loss of intensity due to measurement conditions has to be taken into consideration. All the values given refer to vertical ionization potentials; the peak of maximum intensity is given in the case of bands having a resolved vibrational fine structure. The benzene spectrum was recorded at low resolution for the sake of better comparison.

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Alkaline Earth Metal Halide Hydrates: Use of IR Spectra for Phase Analysis and Determination of Possible Structural Types[1]

By *Heinz D. Lutz, Hans-Jürgen Klüppel,* and *Georg Kho*[*]

Investigations of the lattice vibrations of alkaline earth metal hydroxides have shown[1–3] that IR spectra are much more suitable for the identification and characterization of hydroxides and hydroxide-hydrates than X-ray patterns, which usually contain many lines and, without measurements on single crystals, are only difficultly interpretable. It can now be shown, using alkaline earth metal halide hydrates as example, that lattice vibration spectra also afford a means of classifying compounds having the same stoichiometry into particular structural types and thus considerably simplify the indexing of powder photographs.

Thus it follows from the spectra, and in particular from the number and position of the stretching (3000–3600 cm^{-1}) and bending (1600–1700 cm^{-1}) modes and the librations (300–800 cm^{-1}) of water of crystallization, that the strontium halide hexahydrates $SrCl_2 \cdot 6H_2O$ and $SrBr_2 \cdot 6H_2O$, have, as noted from X-ray crystallographic data[4], the same structure and that the monoclinic barium and strontium halide dihydrates $SrCl_2 \cdot 2H_2O$[4], $BaCl_2 \cdot 2H_2O$[4] and $BaBr_2 \cdot 2H_2O$[5], and $BaI_2 \cdot 2H_2O$[6] belong to three different structural types (Fig. 1).

According to their IR spectra (Fig. 2) the monohydrates of the alkaline earth metal halides, of which we have been able to prepare $SrBr_2 \cdot H_2O$, $SrI_2 \cdot H_2O$, and $BaI_2 \cdot H_2O$ for the first time, are, with the exception of $SrI_2 \cdot H_2O$, all isotypic. The crystallographic data subsequently recorded by us for these compounds, which, according to electron diffraction measurements on $BaCl_2 \cdot H_2O$[7], crystallize in the space group Pnma, are given in the Table.

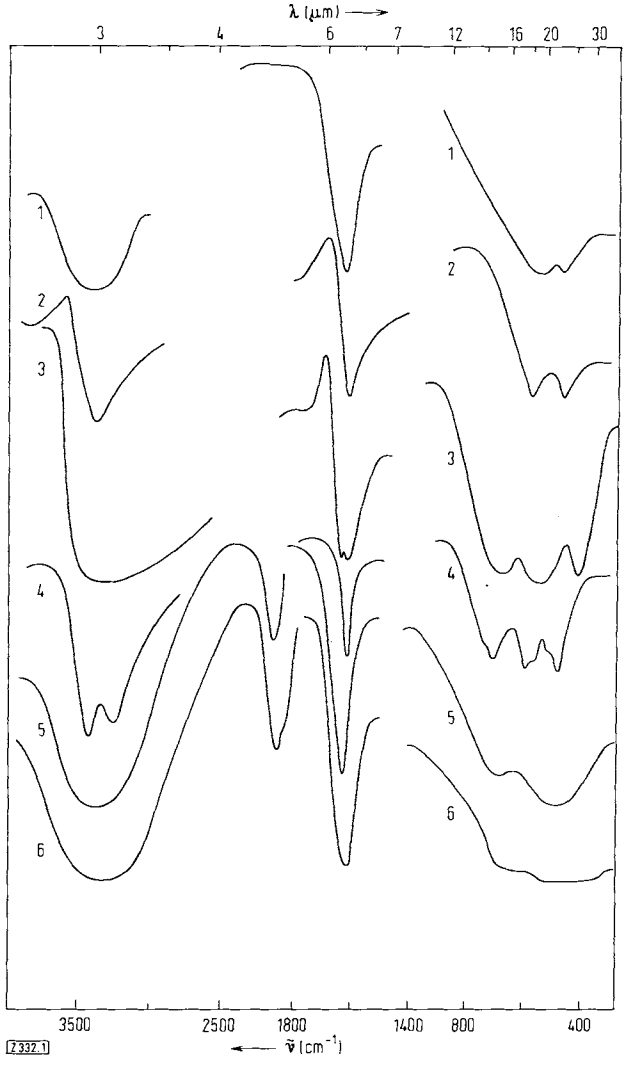


Fig. 1. IR spectra of $BaI_2 \cdot 2H_2O$ (1), $BaBr_2 \cdot 2H_2O$ (2), $BaCl_2 \cdot 2H_2O$ (3), $SrCl_2 \cdot 2H_2O$ (4), $SrCl_2 \cdot 6H_2O$ (5), $SrBr_2 \cdot 6H_2O$ (6).

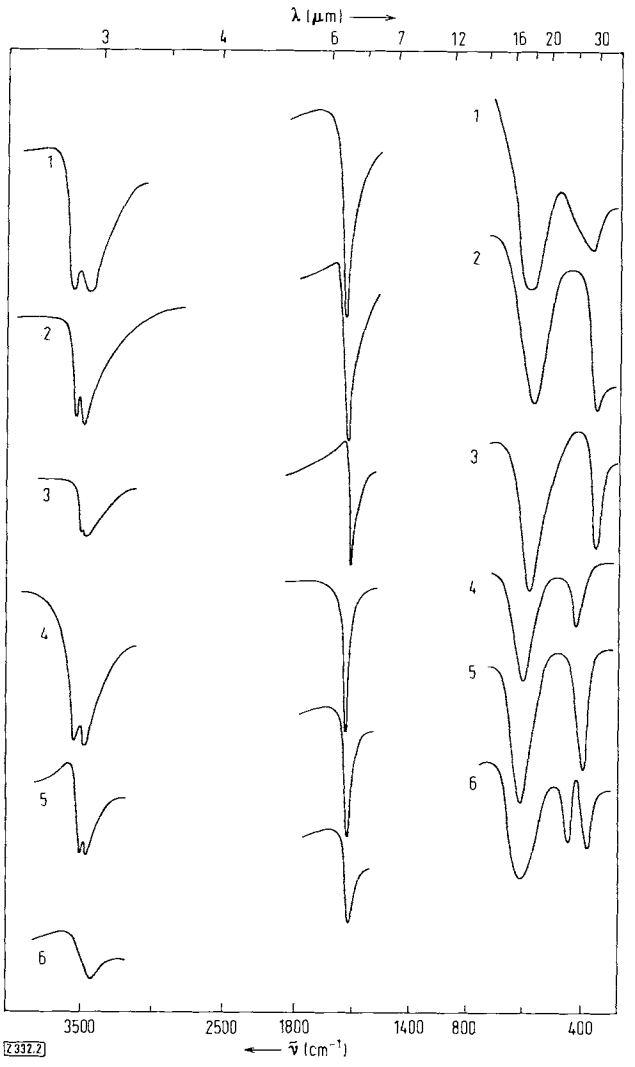


Fig. 2. IR spectra of $BaCl_2 \cdot H_2O$ (1), $BaBr_2 \cdot H_2O$ (2), $BaI_2 \cdot H_2O$ (3), $SrCl_2 \cdot H_2O$ (4), $SrBr_2 \cdot H_2O$ (5), $SrI_2 \cdot H_2O$ (6).

$SrCl_2 \cdot H_2O$ and $SrI_2 \cdot H_2O$ could not be identified X-ray crystallographically. Thus, as has already been established in the case of alkaline earth metal hydroxides[2], compounds of the above type that cannot be identified by X-ray crystallography can be unequivocally characterized by their IR spectra. Just the close range order of a few cells apparently suffices for observation of the lattice vibrations of a structure.

The alkaline earth metal halide monohydrates were prepared by dehydration of hexa- or dihydrates in vacuum at 75–100°C. The preparation of samples for IR spectroscopic measurements (nujol, KBr; Beckman IR 10) and X-ray (powder) crystallography ($Cu_{K\alpha}$) was carried out in a dry-box because some of the compounds are very hygroscopic.

Table. Crystallographic data of alkaline earth metal halide monohydrates (Å).

$MX_2 \cdot H_2O$	*a*	*b*	*c*
$BaCl_2 \cdot H_2O$[7]	4.51	9.02	11.28
$BaBr_2 \cdot H_2O$[7]	4.59	9.41	11.59
$BaI_2 \cdot H_2O$	4.73	9.92	12.15
$SrBr_2 \cdot H_2O$	4.88	8.96	11.47

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[1] Lattice vibration spectra, Part 6. – This work was supported by the Fonds der Chemischen Industrie and the Stiftung Volkswagenwerk. Part 5: *H. D. Lutz, R. Heider,* and *R.-A. Becker,* Spectrochim. Acta, in press.

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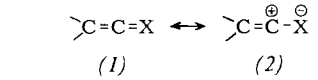
[7] *B. K. Vajnštein* and *Z. G. Pinsker,* Zh. Fiz. Khim. *23,* 1058 (1949).

Cycloadditions of Keteneimines to Ynamines[**]

By *Léon Ghosez* and *Cécilia de Perez*[*]

Experience[1] has well substantiated *Woodward* and *Hoffmann*'s suggestion [2] that ketenes *(1a)* owe their reactivity in

(2+2) cycloadditions to their ability to behave electronically as "pseudo" vinyl cations *(2a)*.

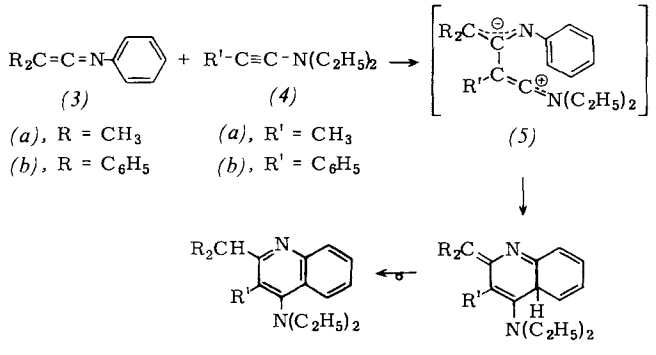


(1) *(2)*

(a), X = O; *(b)*, X = N-R

Substitution of a nitrogen atom bearing various substituents *(1b)* for the oxygen atom in the ketene molecule would offer the interesting possibility of varying the vinylium character of the cumulene *(2b)* and studying the consequences on its behavior in cycloadditions.

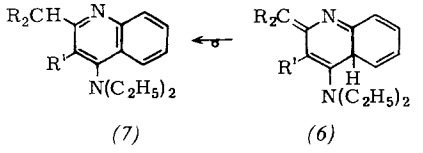
This preliminary report describes the stepwise polar cycloaddition of *N*-aryl and *N*-alkyl-substituted keteneimines to the strongly nucleophilic aminoacetylenes. We have found that *N*-phenylketeneimines *(3a)* and *(3b)* cycloadd to ynamines *(4a)–(4b)* at room temperature to yield the 4-aminoquinoline derivatives *(7a)* to *(7d)* as the sole isolable adducts. This provides a simple synthetic route toward these heterocyclic systems. In contrast the reaction of *N*-methyl-diphenylketeneimine *(3c)* with *(4a)* in acetonitrile is sluggish (7 days) and yields both 1 : 1 and 2 : 1 adducts for which structures *(9)* and *(10)* are proposed mainly on the basis of mass spectral data.



(3) *(4)* *(5)*

(a), R = CH_3 *(a)*, R' = CH_3

(b), R = C_6H_5 *(b)*, R' = C_6H_5



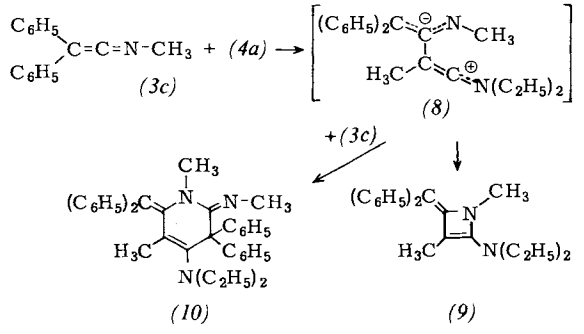
(7) *(6)*

(a), R = R' = CH_3

(b), R = C_6H_5; R' = CH_3

(c), R = R' = C_6H_5

(d), R = CH_3; R' = C_6H_5



(3c) *(8)* *(10)* *(9)*

Cpd.	M.p.(°C) (yield (%))	*m/e*	UV [b]	NMR [c]
(7a)	[a] (85)	256(M^+)	314 (4.12) 309 (3.17) 223 (44.7)	1.05(6 Methyl-H/t); 1.35(6 Methyl-H/d); 2.45(3 Methyl-H/s); 3.32(4 Methylene-H+1 Methine-H/m); 7.40 (2 arom. H/m); 7.90 (2 arom. H/m)
(7b)	137–139 (67)	380(M^+)	322 (5.2) 309 (4.17) 234 (52.7)	1.01(6 Methyl-H/t); 2.38(3 Methyl-H/s); 3.30(4 Methylene-H/q); 5.92(1 Methine-H/s); 7.45(12 arom. H/m); 8.0(2 arom. H/m)
(7c)	156 (61)	442(M^+)	322 (4.5) 234 (54.2)	0.92(6 Methyl-H/t); 2.87(4 Methylene-H/q); 5.45(1 Methine-H/s); 7.00-8.3(19 arom. H/m)
(7d)	69.4 (52)	318(M^+)	320 (4.33) 230 (46.4)	0.95(6 Methyl-H/t); 1.23(6 Methyl-H/d); 2.90(4 Methylene-H + 1 Methine-H/m; ≈ 7.40 (7 arom. H/m); ≈ 8.10 (2 arom. H/m)
(9)	137.3 (35)	318(M^+) 207 205 113	–	0.83(6 Methyl-H/t); 2.13(3 Methyl-H/s); 3.20(4 Methylene-H/q); 3.26(3 Methyl-H/s); ≈ 7.30(10 arom. H/m)
(10)	180.8 (34)	525(M^+) 455 318 207	–	0.50(6 Methyl-H/t); 1.66(3 Methyl-H/s); 2.30(2 Methylene-H/q); 2.70(3 Methyl-H + 2Methylene-H/s + q); 3.22 (3 Methyl-H/s); 6.80–7.70(20 arom. H/m)

[a] B.p. 140–142°C/0.7–0.9 torr.
[b] λ_{max}(nm), $\varepsilon \times 10^{-3}$ (in cyclohexane).
[c] δ values, TMS internal standard (in $CDCl_3$).

In each case, solvents with high dielectric constant were shown to accelerate the reaction: monitoring the reaction by IR showed that, in ether, the formation of *(7d)* required about 3 days, whereas in acetonitrile it was essentially completed after 6–7 h. It is worth noting that these cycloadditions proceed much more slowly than the corresponding reactions involving ketenes[3]. Roughly, it can be said that the reactivity sequence parallels the "vinylium" character of the cumulene:

C=C=O≫C=C=N–aryl > C=C=N–alkyl.

Our observations are consistent with a cycloaddition mechanism involving the initial formation of a stabilized 1,4 dipole *(5)* or *(8)* which either cyclizes to 6 or 4 membered rings *(6)* or *(9)*, or is trapped by a second molecule of keteneimine to yield *(10)*.

2-Benzhydryl-4-diethylamino-3-phenylquinoline (7c). A mixture of *(4b)* (0.329g, 1.9 mmole) and *(3b)* (0.431 g, 1.6 mmole) in acetonitrile (10 ml) was allowed to stand under nitrogen at room temperature; after 10 hours, 0.318 g of crystalline *(7c)* could be filtered off. A further crop of *(7c)* was obtained by evaporation of the filtrate and recrystallization of the resulting residue from ether/pentane. Total yield 0.431 g (61%).

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Anions Derived from PH_3 Complexes: Deprotonation by PH_2^-

By *Gerd Becker* and *E. A. V. Ebsworth*[*].

The complexes $(PH_3)_2Mo(CO)_4$ and $[P_2H_4Mo(CO)_4]_x$ react with potassium in liquid ammonia, giving products which appear to contain anions of the type $[(PH_2)_2Mo(CO)_4]^{-2}$, but in the former case at least the reactions are complicated and the products are difficult to characterize. We have found, however, that phosphane complexes can be deprotonated by potassium phosphide in dimethyl ether. The complex pentacarbonylphosphanemolybdenum(0), for example, reacts quantitatively with KPH_2 in $(CH_3)_2O$ at 0 °C over a period of an hour; phosphane is evolved, and the salt $K[PH_2Mo(CO)_5]$ can be isolated from the resulting solutions as a yellow solid.

$$PH_3Mo(CO)_5 + PH_2^- \rightarrow [PH_2Mo(CO)_5]^- + PH_3$$

The compound has been characterized by its IR and NMR spectra [J(HP) = 160.5 Hz; τ_{PH} = 10.36 in $(CH_3)_2O$] and by analysis. An excess of $PH_3Mo(CO)_5$ yields the binuclear anion complex μ-phosphido-bis(pentacarbonylmolybdate(0))[1]:

$$PH_3Mo(CO)_5 + [PH_2Mo(CO)_5]^- \rightarrow [(CO)_5MoPH_2Mo(CO)_5]^- + PH_3$$

The NMR spectrum of the dimeric anion has been recorded [J(HP) = 249.3 Hz; τ_{PH} = 8.69 in $[D_6]$-acetone]. Signals of minor intensity in the spectrum we assign to a compound like $[PH_3Mo(CO)_4PH_2Mo(CO)_5]^-$ which is formed with the evolution of a small amount of CO.

The salt $K[PH_2Mo(CO)_5]$ reacts slowly with CH_3Cl, giving 50% of the expected yield of $CH_3PH_2Mo(CO)_5$ (characterized spectroscopically by comparison with spectra of authentic samples); reactions with trimethylchlorosilane and with acetyl chloride lead to the formation of a mixture of products $R_nPH_{3-n}Mo(CO)_5$ [R = $(CH_3)_3Si$- or CH_3CO-].

The monomethylphosphane complex $CH_3PH_2Mo(CO)_5$[2] is also deprotonated by KPH_2; 83% of the calc. amount of PH_3 is evolved together with some CH_3PH_2 (17%):

$$CH_3PH_2Mo(CO)_5 + PH_2^- \rightarrow [CH_3PHMo(CO)_5]^- + PH_3$$

An excess of $CH_3PH_2Mo(CO)_5$ yields the bridged anion $[(CO)_5MoPH(CH_3)Mo(CO)_5]^-$. Similar results have been obtained with $(PH_3)_2Mo(CO)_4$ and KPH_2.

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Reactions of Disulfur Difluoride with Fluorosulfonic Acid, Oleum, Boron Trifluoride, and Arsenic Pentafluoride

By *Fritz Seel, Volker Hartmann, Imre Molnar, Rudolf Budenz,* and *Willy Gombler*[*]

Both isomers of disulfur difluoride, SSF_2 and FSSF, dissolve in fluorosulfonic acid and in anhydride-containing sulfuric acid (30% oleum was used) at low temperature with development of a deep yellow color that does not change on prolonged storage at −80 °C. On warming the solution first becomes green before reaching room temperature, then deep blue, and finally, after one hour at room temperature brownish red. UV and ESR spectra indicate that both the blue and the brown solutions contain species made up of sulfur cations as found in solutions of elemental sulfur in oleum[1–7]. Such solutions cannot be prepared in 100% sulfuric acid or from S_2Cl_2. Moreover, it was also found that reaction of S_2F_2 with HSO_3F gives *disulfuryl fluoride* and *thionyl fluoride,* which are also formed by reaction of SF_4 with HSO_3F.

Table. Data for complex cations of sulfur.

$\tilde{\nu}_{max}$(cm^{-1})		g-factor in oleum	Assignment, color	
10600 } 13900 }	[7]	2.0260 [1, 2, 5, 7]	S_n^+,	brownish red [7]
17000	[3, 4, 6, 7]	2.0131 [1, 2, 5, 7]	S_4^+,	deep blue [7]
25000	[4, 7]		S_8^{2+},	yellow [7]
30000	[3, 4, 6, 7]		S_4^{2+},	colorless [6, 7]

IR spectra show SSF_2 and BF_3 to be stable together as gases but not so FSSF and BF_3. A compound *(1)* that is stable only at low temperature could be prepared on a liquid-nitrogen cooled AgCl disk by condensation of S_2F_2 and BF_3; the compound exhibits the IR bands of the tetrafluoroborate ion at 1040 to 1080 cm^{-1} and a characteristic band at 830 cm^{-1}. AsF_5 reacts with S_2F_2 even below −100 °C in the molar ratio 1:1 to give compound *(2)*, which also gives a new IR band at 850 cm^{-1} and the bands characteristic of AsF_6^-. Compounds *(1)* and *(2)* thus appear to have the salt-like structures $S_2F^+\ BF_4^-$ and $S_2F^+\ AsF_6^-$. Further support for this concept comes from the observed catalysis of the conversion of FSSF into SSF_2 by BF_3:

$$FSSF + BF_3 \rightarrow S_2F^+ + BF_4^- \rightarrow SSF_2 + BF_3$$

Remarkably, the band $\tilde{\nu}_3$ (F_{1u}) of the AsF_6^- ion is split into two component bands at 691 and 662 cm^{-1}: This would indicate a lowering of the symmetry of the ion by fluoro bridging. Additional evidence is provided by the width of the band at 850 cm^{-1} which is apparently attributable to the S-F stretching vibration of the S_2F^+ ion. This broad intense band probably masks the S-S frequency. (The maxima of the SF and SS stretching bands of SSF_2 are separated by only 8 cm^{-1}.)

On warming *(2)* is first discolored to ocher yellow. When heated to 100 °C or at room temperature in the presence of AsF_5 it becomes deep blue and on stronger heating finally turns deep red. With regard to their appearance and their intense absorption the blue ($\tilde{\nu}_{max}$ = 17000 cm^{-1}) and the red product resemble the compounds $S_8[AsF_6]_2$ and $S_{16}[AsF_6]_2$ prepared by *Gillespie* and *Passmore*[8] by reaction of sulfur with AsF_5.

They are however mixtures in which $SF_4 \cdot AsF_5 = SF_3^+AsF_6^-$ *(3)* ($\tilde{\nu}_{SF} = \tilde{\nu}_3(E)$ = 926 cm^{-1}; δ_{FS} = −30 ppm from $CFCl_3$ in SO_2 solution) can be detected by IR and NMR spectrometry, and the blue and brownish red radical ion of sulfur by ESR spectrometry. Decomposition of *(2)* thus differs from the disproportionation of disulfur difluoride into sulfur and SF_4 in that complex sulfur cations are formed instead of molecular sulfur because the initially formed negative charge carrier AsF_6^- is extremely stable. The finding that decomposition of *(2)* does not give free AsF_5 indicates that $S_4[AsF_6]_2$ *(4)* is formed as main decomposition product together with *(3)*.

$$12\ (2) \rightarrow 3\ (3) + 3\ (4) + S_8[AsF_6]_2 \text{ or } 2\ S_4[AsF_6]$$

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In liquid SO_2 reaction of S_2F_2 with AsF_5-proceeds just as fast as the reaction with fluorosulfonic acid; after initial red coloration a deep blue solution is formed. ^{19}F-NMR signals indicate unstable intermediates, which rapidly exchange fluorine, and the presence of the end products SF_3^+ and AsF_6^-.

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P–N Cleavage in Tris(dimethylamino)phosphanecarbonyl Complexes of Molybdenum(0)[1]

By *Mathias Höfler* and *Wolfgang Marre*[*]

The P–N bonds in $(PF_3)_xNi(PF_2NR_2)_{4-x}$ (x = 0,1,2,3) can be cleaved by HCl to give the corresponding PF_2Cl complexes[2]. Since trisaminophosphanes are excellent complexing ligands (their complexing behavior is similar to that of triphenylphosphane[3]), it was considered of interest to investigate the applicability of such reactions to aminophosphanemetal carbonyls. As model compounds for the investigation we chose $Mo(CO)_5P(NMe_3)_3$ *(1)* and *trans*-$Mo(CO)_4[P(NMe_2)_3]_2$ *(2)* (Me = CH_3).

(1) was treated with liquid HCl in an autoclave at 20 °C without addition of solvent: purification of the reaction products by chromatography afforded a colorless crystalline product in *ca.* 60% yield which was identified by elemental analysis and IR spectroscopy as pentacarbonyltrichlorophosphanemolybdenum(0) *(3)*.

$$\underset{(1)}{Mo(CO)_5P(NMe_2)_3} + 6HCl_{(g)} \rightarrow \underset{(3)}{Mo(CO)_5PCl_3} + 3[H_2NMe_2]Cl\ (A)$$

Introduction of HCl gas into a pentane solution of the complex *(1)*, on the other hand, led to a mixture of *(1)*, $Mo(CO)_5PCl(NMe_2)_2$, $Mo(CO)_5PCl_2NMe_2$, and *(3)*. The cleavage reaction (A) could also be used for the analogous synthesis of *trans*-$Mo(CO)_4(PCl_3)_2$ from *(2)*.

In order to check whether the cleavage reaction – which was carried out for the first time on phosphane-substituted metal carbonyls – could also be used for the preparation of PBr_3 and PI_3 complexes we investigated the reaction of *(1)* with HBr and with HI. The reaction with HBr according to the method (A) afforded $Mo(CO)_5PBr_3$ in *ca.* 50% yield; reaction with HI in pentane at −20 °C gave a disubstitution product in 30% yield.

$$(1) + 4HI \longrightarrow \underset{(4)}{Mo(CO)_5PI_2NMe_2} + 2[H_2NMe_2]\,I$$

If the reaction temperature is increased to −5 °C, a mixture of substances can be isolated after 4 hours that consists of 70% of *(4)* and 30% of $Mo(CO)_5PI_3$ *(5)*. However, since the PI_3 complex *(5)* decomposes in solution at room temperature, attempts to obtain pure *(5)* by further reaction at an increased temperature have so far failed.

The reactivity of the halogen hydracid HX increases in the series HCl < HBr < HI. That the reaction with HI – in contrast to HCl and HBr – is not quantitative is mainly due to steric hindrance.

The spectroscopic and physical properties of the PX_3 complexes prepared by us are in agreement with those reported by other authors[4, 5].

Of such PX_3 complexes, those with X = Cl are the most suitable for the synthesis of further phosphane complexes because of the reactivity of the P–Cl bond and the low nucleophilicity of the chloride ion. They react with moderately weak and very weak bases with replacement of Cl. Thus, reaction of *(3)* with water-free methanol proceeds as follows:

$$(3) + 3CH_3OH \longrightarrow \underset{(6)}{Mo(CO)_5P(OCH_3)_3} + 3HCl$$

However, the reaction is not complete until after 3 hours and is thus considerably slower than the methanolysis of free PCl_3.

Since aminophosphane complexes in general are readily accessible and stable they open up a new route for the synthesis of PX_3 complexes (X = Cl,Br,I), which can be used for the preparation of other phosphane complexes.

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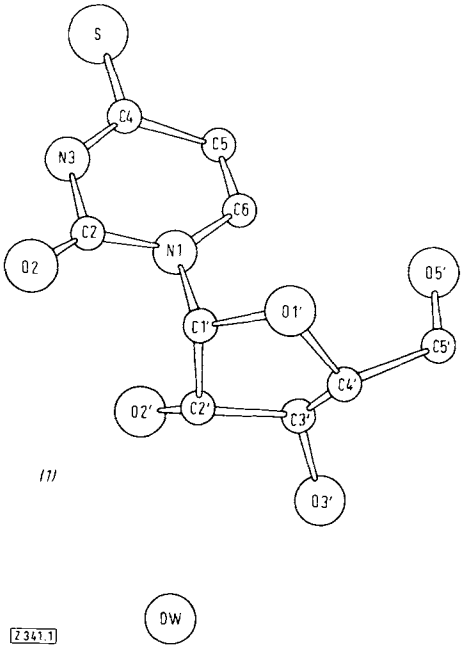
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Conformation of the Arabinonucleoside 1-β-D-Arabinofuranosyl-4-thiouracil

By *Wolfram Saenger* and *Volker Jacobi*[*]

In connection with studies of the behavior of thiopyrimidine nucleotides toward various polymerizing enzymes[1] our interest has been directed to the properties[2] of 1-β-D-arabinofuranosyl-4-thiouracil *(1)* and its phosphorylated derivatives. *(1)* differs from 4-thiouridine[3] only in the position of the 2'-hydroxyl group.

The conformation of the arabinose residue in *(1)* was found to be not unusual.



(1)

Fig. Structure of 1-β-D-arabinofuranosyl-4-thiouracil *(1)*, projection along the crystallographic *a* axis.

Compound *(1)* crystallizes from water in the form of thick plates of monoclinic space group $P2_1$ and unit cell dimensions a = 4.787, b = 15.060, c = 8.661 Å; β = 73.0°. The density of the crystals indicated that the nucleoside was in the form of its monohydrate. The intensities of approximately 2000 reflections were measured on an automatic diffractometer (Mo radiation) and corrected for geometric factors. The position of the C4-S vector could be obtained from a sharpened Patterson synthesis with removed origin; once this information had been

obtained, the complete structure (Fig. 1) could be derived from two Fourier syntheses. The atomic parameters were subjected to isotropic full-matrix refinement by the method of least squares until an R factor of 9% was reached. At this stage the following features became apparent (see Fig. 1):

a) In *(1)* the dihedral angle C2'-C1'-N1-C6[3] is −80° (*i.e.* the bond N1-C6 is rotated by 80° in an anticlockwise direction with respect to the bond C1'-C2'). Hitherto, all pyrimidine nucleosides apart from 4-thiouridine have been found to have this *anti* conformation[4] in which the O2 atom points away from the sugar.

b) As in 4-thiouridine, 3'-*O*-acetyl-4-thiothymidine[5], 2,4-dithiouridine[6], and 1-methyl-4-thiouracil[7], the 4-thiouracil residue is in the keto, keto form. The atoms of the heterocycle are substantially coplanar.

c) In nucleosides the sugars usually have an "envelope" configuration with C2' or C3' displaced about 0.5 Å from the plane through the other four atoms of the five-membered ring. In the arabinose present in *(1)*, C3' is about 0.6 Å away from the plane and on the same side as C5' – the sugar residue thus has the C3'-*endo* conformation.

The *cis*-diol group in ribosyl residues of comparable C3'-*endo* conformation has a dihedral angle O2'-C2'-C3'-O3', of about +50°. In the arabinose residue, however, this angle is about −80°, *i.e.* the C3'-O3' bond is rotated in an anticlockwise direction relative to the C2'-O2' bond.

The dihedral angle N1-C1'-C2'-O2' is also an important factor in any comparison between the structures of the ribose and the arabinose residues. In the C3'-*endo* ribonucleosides this angle is about −140°; however, in *(1)* it is only −29°, *i.e.* in the former case the C1'-N1 and C2'-O2' are *"trans"* (*trans*-planar or -*anti*-clinal (-ac)[8], and in the latter case they are *"cis"* (*cis*-planar or -*syn*-periplanar (-sp)[8]).

The position of O5' relative to the arabinose is given by the dihedral angles O5'–C5'–C4'–O1' and O5'–C5'–C4'–C3'[9] which are *ca.* −55° and 62° respectively in the present case. The atom O5' thus lies above the sugar residue, a position that is preferred in ribonucleosides.

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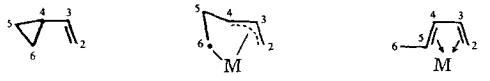
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Complex Bonding of a Vinylcyclopropane Group of Bullvalene to a Transition Metal *via* a π-Allyl and a σ Component[1]

By *Rudolf Aumann*[*]

Reaction of cyclopropane with H_2PtCl_6 yields a brown complex[2] containing a C_3Pt ring[3]. Analogous ring systems incorporating rhodium are also known[4]. Vinylcyclopropane *(3)*[5] and methylenecyclopropane[6] form stable π-allyl-palladium complexes, apparently by ring opening of the postulated edge-coordination complexes[7]. The action of $Fe_2(CO)_9$ on cyclopropylstyrene[8] and spiro[2.4]hepta-4,6-diene[9] furnishes substituted diene-$Fe(CO)_3$ complexes. Manganese, rhenium, iron, and iridium have been reported to give very stable cyclopropylcarbonyl complexes, the manganese compound affording a π-allyl derivative on decarbonylation[10].

The present communication reports on the first example *(2)* of complex formation by a vinylcyclopropane group *(3) via* a π-allyl and a σ component *(4)* with a $Fe(CO)_3$ unit.



(3) *(4)* *(5)*

Previous investigations[8] on this topic led to the isolation of substituted butadiene-$Fe(CO)_3$ complexes *(5)*. An intermediate *(4)* was mentioned. System *(4)* proves to be stable if C^5 is the bridgehead C atom of a polycyclic system as in complex *(2)*. The halflife of *(2)* on thermal decomposition at 135 °C in *n*-octane is about 20 h. Complex *(2)*, m.p. 133–134 °C, is the major product of the reaction between bullvalene *(1)* and $Fe_2(CO)_9$[11], in which six isomeric complexes of composition $C_{10}H_{10}Fe_2(CO)_6$ and a complex $C_4H_4Fe_2(CO)_6$ are also formed as minor products.

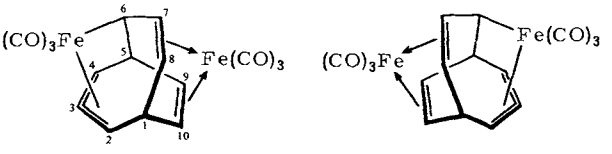


Fig. 1. The enantiomers of compound *(2)*.

Since *(1)* contains both an unconjugated diene unit and a vinylcyclopropane group in a position favorable for complex formation, it can form both 1,4-diene complexes and vinylcyclopropane complexes, depending upon the metal system used. Thus the 1,4-diene partial structure bonds to $Mo(CO)_4$ or $W(CO)_4$ groups, leaving the cyclopropane ring intact[12], while cleavage of the cyclopropane ring occurs on bonding to metal systems such as $Fe(CO)_3$ that are richer in electrons.

Perturbation calculations on a simple Hückel model of butadiene show that an increase in the distance C^4–C^6 in *(4)* leads to a decrease in the energy of the antibonding orbitals, and an increase in energy of the bonding orbitals. This would indicate more extensive back donation from metal to ligand in *(2)* than in butadiene-$Fe(CO)_3$ *(6)*. This effect can be detected experimentally by an increase in the ν_{CO} frequency in the IR spectrum of *(2)* compared to that of *(6)*:

ν_{CO} in cm^{-1} (hexane as solvent)

(6): 2054, 1989, 1979
(2): *(a)* 2054, 1996, 1992;
(b) 2024, 1980, 1964.
a = 2,3,4,6-*tetrahapto*-$Fe(CO)_3$
b = 7,8,9,10-*tetrahapto*-$Fe(CO)_3$

The CH skeleton of *(2)* was determined by ^{1}H-NMR analysis, including double resonance and tickling experiments, on the basis of the observed coupling pattern[13]. Since the relative positions of the resonance signals are strongly dependent upon the solvent the measurements were carried out both in CS_2 and in C_6H_6 solutions.

The protons H^2,H^3,H^4 form an allyl system whose chemical shifts[14] $H^2 = 5.15\,\tau$, $H^3 \approx H^4 = 5.4\,\tau$[15] correspond to those found in similar complexes[16]. H^2 is strongly coupled to H^1 = 6.13 τ ($J_{1,2} \approx 8.5$ Hz), and $H^{3,4}$ to $H^5 = 7.13\,\tau$. $H^{9,10} = 6.95\,\tau$

and H^1, H^5 give an AA'CX system ($J_{5,9}$ = 7.2 Hz; $J_{9,10}$ = 4.8 Hz; $J_{5,10} = J_{1,9} = -1.2$ Hz; $J_{1,5}$ = 2.4 Hz)[17]. The measured coupling constants $J_{6,7} = J_{7,8} = J_{1,8}$ = 7.5 Hz (H^7 = 6.68 τ, H^8 = 6.29 τ) are in good agreement with the values expected. $J_{5,6}$ = 11.5 Hz indicates a small dihedral angle between H^5 and H^6 and thus also a close proximity of C^6 and the allyl system. As expected, H^6 = 8.58 τ is strongly shielded by the metal.

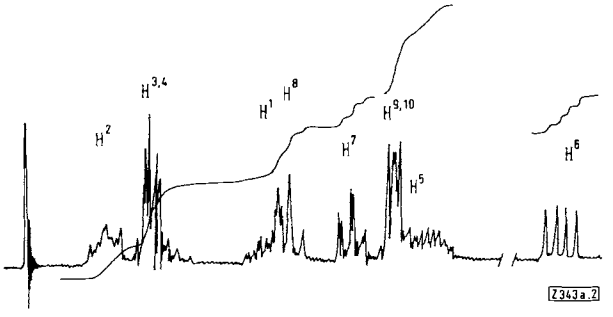


Fig. 2. ^{1}H-NMR spectrum of *(2)* in CS_2 solution; 100 MHz; CH_2Cl_2 = 4.70 τ as internal standard.

The enantiomers of the racemate formed on synthesis of *(2)* are configurationally stable on the NMR time scale.

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[1] Transition metal complexes of $(CH)_n$ compounds, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft. I am grateful to Dr. *D. Wendisch*, Ing. Abt. AP 10, E 41, Bayer-Leverkusen, for measuring NMR spectra at 220 MHz, and to BASF, Ludwigshafen, for the supply of cyclooctatetraene. – Part 1: *R. Aumann*, Angew. Chem. *82*, 810 (1970); Angew. Chem. internat. Edit. *9*, 800 (1970).

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[11] Cf. *G. N. Schrauzer, P. Glockner, K. I. G. Reid*. and *I. C. Paul*, J. Amer. Chem. Soc. *92*, 4479 (1970). The authors isolated bicyclo[4.2.2]-deca-2,4,7,9-tetraene-$[Fe(CO)_3]_2$ as the sole product of this reaction. In our investigation this compound represented only about 20% of the product mixture.

[12] Cf. ref. [1].

[13] X-ray structure analysis is currently being performed by Dr. *G. Huttner*, München.

[14] 5% solution in CS_2; 100 MHz; CH_2Cl_2 = 4.70 τ.

[15] Estimated from the spectrum.

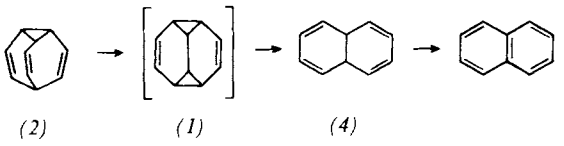
[16] *R. Aumann*, unpublished.

[17] Coupling constants calculated.

A Stable Bis(tricarbonyliron) Complex of Tetracyclo[4.4.0.0^{5,7}.0^{2,10}]deca-3,8-diene and Its Dynamic Behavior in Solution[1]

By *Rudolf Aumann*[*]

Tetracyclo[4.4.0.0^{5,7}.0^{2,10}]deca-3,8-diene *(1)* has been postulated by *Schröder* as an intermediate in the thermally induced conversion of bullvalene *(2)* into naphthalene[2], and has recently been enriched to 40–50% in the photostationary mixture of hydrocarbons formed on low-temperature photolysis of *(2)*[3,4].



(2) *(1)* *(4)*

The present communication reports on a stable iron complex *(3)* derived from *(1)* by complex bonding of the two vinylcyclopropane partial structures[1]. Complex *(3)*, m. p. 172 °C, is formed in the thermal reaction of *(2)* with $Fe_2(CO)_9$ along with six isomeric compounds of composition $C_{10}H_{10}Fe_2(CO)_6$ and a compound $C_4H_4Fe_2(CO)_6$[1].

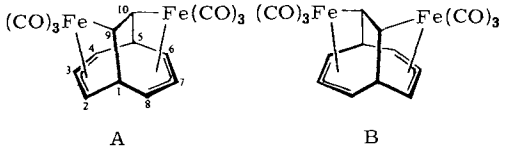


Fig. 1. The enantiomers A and B of compound *(3)*.

The CH skeleton of *(3)* was analyzed by ^{1}H-NMR employing double resonance and the usual calculations. Mössbauer measurements showed both iron atoms to have the same s-electron density at the nucleus (IS = 0.215 ± 0.003 mm/s) and the same field gradients (QS = 0.761 ± 0.003 mm/s)[6], thus establishing the identity of the chemical environments of both iron atoms.

As a result of the C_{2v} symmetry of the molecule, the NMR parameters of *(3)* show a pairwise equivalence: $H^4 = H^8$ = 5.29, $H^2 = H^6$ = 5.18, $H^3 = H^7$ = 5.66, $H^1 = H^5$ = 7.04, $H^9 = H^{10}$ = 8.08 τ[7]. H atoms 2,3,4 and 6,7,8 appear as a somewhat distorted allyl system in the ^{1}H-NMR spectrum recorded at 0 °C. Coupling constants $J_{2,3} = J_{6,7}$ = 8.0, $J_{3,4} = J_{7,8}$ = 7.0, $J_{1,2} = J_{5,6}$ = 7.0, and $J_{4,5} = J_{1,8}$ = 8.0 Hz, and the chemical shifts of the allyl protons in the NMR spectrum agree with the values found for similar iron complexes[1,5]. The

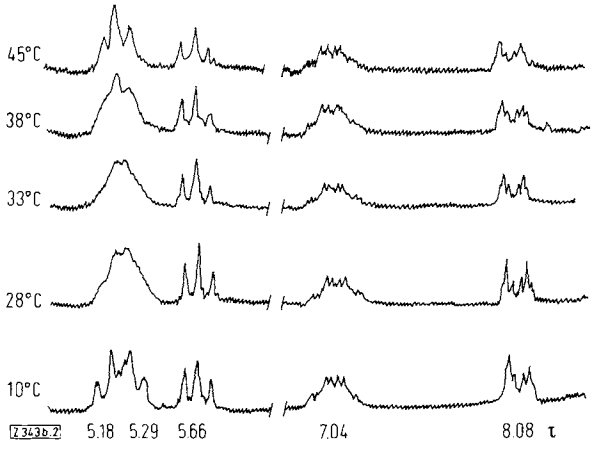


Fig. 2. ^{1}H-NMR spectrum of *(3)* at various temperatures (saturated solution in [D_2]methylene chloride; 100 MHz).

chemical-shift of $H^{9,10}$ can readily be explained for the given skeleton by assuming a coordination of C^9 and C^{10} to the metal, thus leading inevitably to the structure shown in Fig. 1.

The AA'XX' system formed by protons 9,10 and 1,5 was analyzed by computer. The strong vicinal coupling $J_{1,9} = J_{5,10} = 10$ Hz indicates a small dihedral angle between H^5 and H^{10}. Consideration of models clearly shows that this signifies spatial proximity of C^9 and $C^{2,3,4}$ and of C^{10} and $C^{6,7,8}$[8].

The ^{1}H-NMR spectrum of *(3)* recorded at 0 °C is a limiting spectrum since further lowering of the temperature causes no change in the shape of the signals. On warming, however, increasingly rapid exchange of the magnetic environments of $H^2 \rightleftharpoons H^4$ and $H^6 \rightleftharpoons H^8$ becomes evident from signal broadening. Above ≈ 45 °C these resonance signals are averaged (Fig. 2)[10].

This effect is tentatively interpreted as mutual interconversion of the enantiomers A and B (Fig. 1). Of all conceivable exchange processes, this would involve the minimum possible change in the relative spatial positions of all the atoms involved. Racemization entails inversion at C^9 and C^{10} (Fig. 1). The free energy of activation $\Delta G^{\neq}$ measured at the coalescence temperature in methylene chloride is 15.9 ± 0.5 kcal/mole[9]. A value of $\Delta G^{\neq} \approx 16$ kcal/mole was obtained for a similar racemization of a $C_{10}H_{10}$ skeleton attached to a $Fe_2(CO)_6$ group[5].

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[1] Transition metal complexes of $(CH)_n$ compounds, Part 3. This work was supported by the Deutsche Forschungsgemeinschaft. I am also grateful to BASF, Ludwigshafen, for the supply of cyclooctatetraene. – Part 2: *R. Aumann*, Angew. Chem. *83*, 175 (1971); Angew. Chem. internat. Edit. *10*, 188 (1971).

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[5] *R. Aumann*, unpublished.

[6] The Mössbauer spectrum was kindly recorded by Dr. *B. Hentschel*, Münster.

[7] Saturated solution of *(3)* in [D_2]methylene chloride; 100 MHz; reference signal CH_2Cl_2 = 4.70 τ.

[8] An X-ray structure analysis is currently being performed by Dr. *I. C. Paul*, Urbana, Ill.

[9] The calculation of errors is based on the assumption of an inaccuracy in the determination of the coalescence temperature of 33 ± 5 °C.

[10] An accidental overlap of signals due to the temperature shift was excluded by careful calibration of the temperature dependence of the chemical shifts.

Isobullvalenebis(tricarbonyliron)[1]

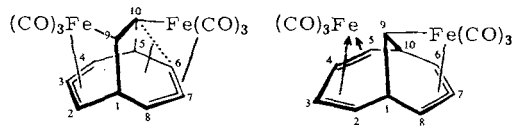
By *Rudolf Aumann*[*]

Isobullvalene *(1)* has recently been synthesized by *Masamune et al.*[2] and *Katz et al.*[3]. This communication reports on a metal complex *(4)* derived from *(1)* by complex bonding of the conjugated diene- and vinylcyclopropane units[4] to $Fe(CO)_3$ groups.



(1) *(2)*

(4), m.p. 123 °C, is formed quantitatively at 120 °C in the thermally induced skeletal rearrangement of a $Fe_2(CO)_6$ complex *(3)* of tetracyclo[4.4.0.0^{5,7}.0^{2,10}]deca-3,8-diene *(2)*[5].



(3) *(4)*

The CH skeleton of *(4)*, like that of the complex *(3)*, was determined from the ^{1}H-NMR spectrum. The coupling constants $J_{2,3} = J_{4,5} = 8.0$, $J_{3,4} = 5.0$ Hz calculated from the AA'XX' system of the protons 2,3,4,5 agree with the values expected for such a structure, as do $J_{1,2} = J_{5,10} = 8.0$ Hz[6]. The arithmetic mean $\bar{H} = 5.59$ τ of the chemical shifts[7] of $H^{3,4} = 4.80$ τ and $H^{2,5} = 6.38$ τ corresponds to the arithmetic mean of the chemical shifts of the allyl protons $H^{6,7,8} \approx 5.6$ τ[8]. As expected, $H^9 = 9.19$ τ is strongly shielded by the metal. The chemical shift of the bridgehead protons $H^{1,10} = 7.19$ τ do not differ appreciably from the value observed in the case of *(3)*[4].

Confirmatory evidence for structure *(4)* comes from the long-range coupling of H^6 and H^8 to H^9 ($J_{6,9} = J_{8,9} = 1.4$ Hz) and the absence of any such coupling of H^2 and H^5 to H^9 in the ^{1}H-NMR spectrum, as well as from the mass spectrum and elemental analysis.

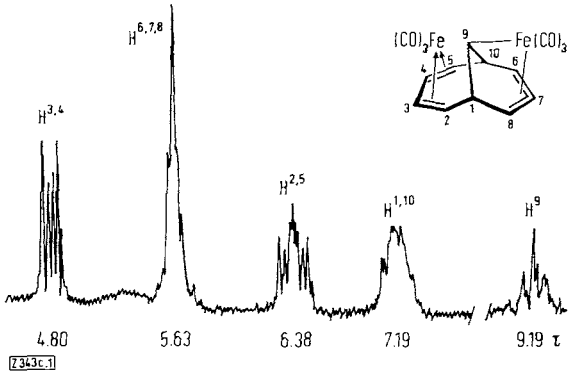


Fig. ^{1}H-NMR spectrum of *(4)*. Solution in $CHCl_3$; TMS as internal standard; 100 MHz.

Isomerization of *(3)* to *(4)* proceeds by way of a 1,2-rearrangement of the carbon skeleton, in which one of the two seven-membered rings is transformed into a six-membered ring that is coordinated to a $Fe(CO)_3$ group *via* the π-allyl system $C^{6,7,8}$ and a two-center bond (from C^9). No further 1,2-rearrangement to give a bond between C^2 and C^9, thus affording the known compound 9,10-dihydronaphthalene-[$Fe(CO)_3$]$_2$ *(5)*[9], was

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[5] Cf. ref. [1].

[6] *R. Aumann*, unpublished results.

[7] 10% solution in chloroform; TMS as internal standard.

[8] Estimated from the spectrum.

[9] Cf. *G. N. Schrauzer, P. Glockner, K. I. G. Reid*, and *I. C. Paul*, J. Amer. Chem. Soc. *92*, 4480 (1970).

found to occur on heating of *(4)* to 180 °C. It is therefore clear that complex *(4)* cannot be an intermediate of the thermally induced (180 °C) isomerization of bicyclo[4.2.2]deca-2,4,7,9-tetraene-$[Fe(CO)_3]_2$[9] to *(5)*.

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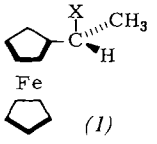
The Retentive Nucleophilic Substitution of (*R*)-α-Ferrocenylethyl Acetate

By *George W. Gokel* and *Ivar K. Ugi*[*]

It is well known that reactions of esters with nucleophiles proceed *via* an additive attack of the nucleophile on the ester carbonyl followed by elimination of the alkoxide moiety[1], leading to cleavage of the acyl-alkoxy bond. Recently, *Richards et al.*[2] demonstrated that ethanolysis of α-ferrocenylethyl acetate afforded 1-ethoxy-1-ferrocenylethane and acetic acid. This result indicates that the reaction proceeds by a mechanism other than that already known.

Our interest in the α-ferrocenylethyl system arises from its potential as a model system of optically active amine components for stereoselective four component syntheses of peptides[3]. This synthesis necessitates cleavage of the auxiliary group introduced by the amine component from the four component condensation product such that the chiral amine can be regenerated in its original configuration. The stereochemical integrity of the α-ferrocenylethylcarbonium ion[4] prompted the investigation reported here.

Since α-ferrocenylethyl compounds *(1)* with a strong leaving

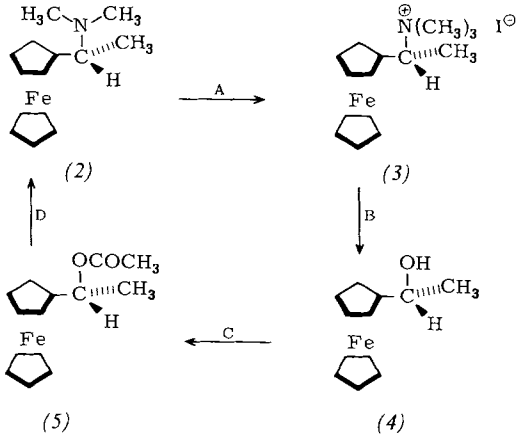


(1)

group, for example, X = Cl[5], have a pronounced tendency to eliminate HX leaving vinyl ferrocene, we attempted to find a suitable group, X, such that the transformation

(1), X = OH → *(1)*, X = NH_2

proceeds in good yield and is easy to carry out. We found that the reaction cycle A→D proceeds in good chemical yield at all stages and with complete configurational retention throughout the cycle.

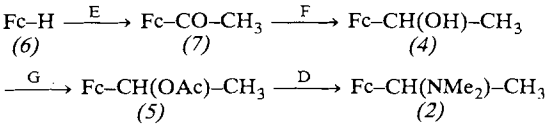


(2): Preparation and resolution [6]: $[\alpha]_D^{25} = +14.1°$ (*c* = 1.5, ethanol); after reaction cycle: $[\alpha]_D^{25.2} = +14.0°$ (*c* = 2.3, ethanol).
(3): $[\alpha]_D^{24.2} = +40.8°$ (*c* = 1.2, methyl cellosolve) [5].
(4): $[\alpha]_D^{25} = -28.9°$ (*c* = 1.7, benzene).
(5): $[\alpha]_D^{25.4} = -27.1°$ (*c* = 1.4, ethanol).

A: Ref. [9]; B: Stir in 1:1 aqueous acetonitrile at *ca.* 20 °C for 15 hours [7] yield = 90%; C: Ref. [8]; D: Stir at *ca.* 20 °C with five equivalents of dimethylamine for 15–20 hours in aqueous methanol, yield = 84%.

The transformation *(4)*→*(5)*→*(3)* is also important for the synthesis of *(2)*, a key compound in the stereochemistry of ferrocene derivatives. To our knowledge, *(2)* is the only known ferrocene derivative whose racemate gives both antipodes in good yield, and which can be transformed with a high degree of stereoselectivity into ferrocene derivatives with a plane of chirality.

The substitution of the acetate by a dimethylamino group proceeds in excellent yield and provides for the synthesis of *(2)* from *(4)* by an alternative to the phosgene method[6].



Fc = $C_{10}H_9Fe$–; E: Acetyl chloride, aluminum chloride in dichloromethane for 2 hours at 0 °C [9], yield = 95%; F: Sodium bismethoxyethoxy aluminate [10] in benzene (1 M) for 1 hour, yield = 90%, G: boil with 5 equiv. acetic acid in benzene for 3 hours, yield = 96%

The replacement of the acetoxy group in *(5)* by ammonia proceeds in only 45% yield.

Pertinent experiments with other easily prepared esters of α-ferrocenylethanol are in progress.

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University Park, Los Angeles, Cal. 90007 (USA).

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Cycloadditions of Phosphonodithioic Anhydrides; Formation of Dienephosphinodithioic Acids

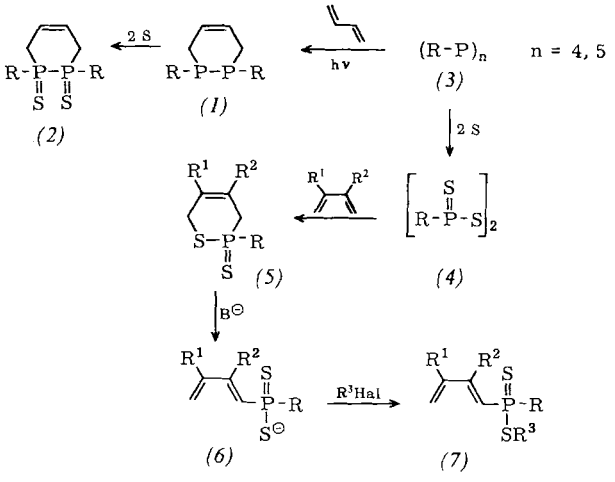
By *Alfred Ecker, Immo Boie*, and *Ulrich Schmidt*[*]

In connection with our studies of the photochemical reaction between cyclophosphines and dienes[1,2] we have treated the reaction product with sulfur in order to characterize the resulting 3,6-dihydro-1,2-diphosphorins *(1)* as stable disulfides *(2)*. In so doing we found that unreacted cyclophosphine *(3)* forms a phosphonodithioic anhydride *(4)* that adds to an excess of diene to give the six-membered heterocyclic compound *(5)* in a reaction that proved to be almost universally applicable. To carry

out the addition, the dithioic anhydride (which is usually readily accessible from phosphonothioic dichloride and H_2S[3]) is heated for several hours with an excess of the diene in an autoclave at about 100 °C.

The structures of the adducts were deduced from their NMR spectra. *(5f)* in CCl_4: multiplet at δ 1.89 (3H), doublets (J = 13 Hz) at δ 1.99 (3H) and 2.80 (2H), a doublet with fine structure at δ 3.54 (2H), and a multiplet at δ 5.86 (1H). The absence of γ-coupling with the phosphorus indicates that the methyl group is in position 5. Coupling of this kind is observed for 4-methyl groups, *e.g.* in *(5c)* and *(5j)*.

On reaction with strong bases in aprotic solvents (*e.g.* NaH in diglyme) initial metalation is followed by ring cleavage to give the dienephosphinodithioic acids *(6)* which react *in situ* with alkyl halides to give the esters *(7)*.



(5)	R	R^1	R^2	Yield (%)	M.p. (°C)	B.p. (°C/torr)
(a)	Phenyl	H	H	65	70	
(b)	Phenyl	H	CH_3	88	33	
(c)	Phenyl	CH_3	CH_3	90	62	
(d)	Cyclohexyl	H	H	75	51	
(e)	Cyclooctyl	H	H	76	61	
(f)	Methyl	H	CH_3	76	60	107/0.01
(g)	Isopropyl	H	H	86		101/0.015
(h)	Thienyl	H	H	70		160/0.001
(i)	Thienyl	H	CH_3	81	39	
(j)	Thienyl	CH_3	CH_3	82	85	
(k)	Isobutyl	H	H	97		135/0.4
(l)	Isobutyl	CH_3	CH_3	53		144/0.4

Synthesis of (5j):

Thiophene-2-phosphonodithioic anhydride[4] (30 g) and 2,3-dimethylbutadiene (50 ml) are heated together for 2 h at 100 °C in an autoclave. The product crystallizes on cooling of the reaction mixture. Recrystallization from ethyl acetate affords colorless crystals (36 g) having m.p. 85 °C.

Cleavage of (5j) with NaH and esterification of the butadiene-phosphinodithioic acid (6j):

Compound *(5j)* (5.2 g) and NaH (0.5 g) are stirred for 2 h at 75 °C in anhydrous 1,2-dimethoxyethane (60 ml). *p*-Nitrobenzyl bromide (4 g) in ether (50 ml) is then added to the reaction mixture and the resulting NaBr is filtered off immediately. The solution is evaporated down to a volume of 20 ml and the product filtered off with suction after standing for several days. Recrystallization from ether furnishes 3.8 g of *p*-nitrobenzyl-*P*-(2,3-dimethylbutadienyl)-*P*-(2-thienyl)phosphinodithioate *(7j)*.

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ESR Investigations of an Oscillating Redox System[**]

By *Horst Frühbeis* and *Albert Röder*[*]

Periodic processes play an important role in biological systems[1]. In addition to oscillating enzymatic systems[2], several purely chemical systems have been described which oscillate in an homogeneous medium[3]. One of these – the oxidation of malic acid by bromate in acid medium, which is catalyzed by Mn^{2+} ions and occurs in a limited concentration range as an oscillating redox system[3] – was chosen by us as a model reaction on the following grounds:

1. Despite the unphysiological pH range (see below) and oxidation pool (bromate) two important biochemicals are involved (malic acid and Mn^{2+}).

2. In ESR spectroscopy we had a "probe" at hand for specific measurement of the concentration of the Mn^{2+} catalyst. Its characteristic six-line spectrum is not influenced under the conditions of the oscillating mixture, either by malic acid and bromate concentration or by the concentration of H^+ ions.

3. We found (Fig. 1) that the catalyst participates in the oscillation.

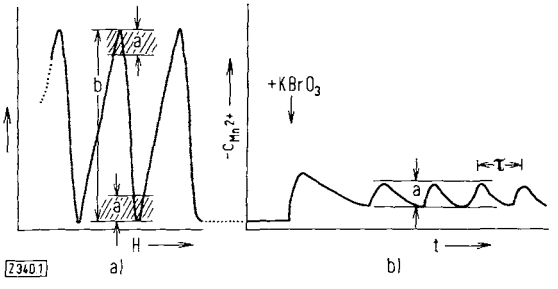


Fig. 1. Calculation of the oscillating portion of the Mn^{2+} ions (b = 100%, $2a$ = 25%). a) Derivation of the intensity of the ESR absorption line as a function of the magnetic field, b) concentration of Mn^{2+} as a function of time (magnetic field constant). Mixture: 20ml 10^{-2}M $MnSO_4$ in 2N H_2SO_4, 50ml 2N H_2SO_4, 40ml 1M malic acid and 40ml 0.25M aqueous $KBrO_3$ solution (see arrow). Varian x band spectrometer, Mod. 125, Amp. 1000, H_0 3155 gauss, rate of pen recorder 12.4 cm/min.

Measurements were carried out at the maximum (or minimum) of one of the six absorption lines of Mn^{2+} (Fig. 1a) at constant field; the Mn^{2+} concentration was recorded as a function of time (Fig. 1b). The reaction mixture was mixed outside the cuvet through which it was subsequently pumped by means of an all-teflon pump.

With this arrangement we were able to record the initial phase of the oscillation (Fig. 1b). It can be seen from the same figure that maximally about 25% of the Mn^{2+} ions occur in a higher oxidation state at the concentrations of the redox pool quoted. The length of the period τ is influenced by various reaction mixture parameters, the hydrogen ion concentration playing a significant role. The period is short at high H^+ ion concentration and long at low H^+ ion concentration. Under the experimental

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conditions quoted below it varies between *ca.* 30 sec (on addition of 20 ml 8N H_2SO_4) and 10 minutes (on addition of 20 ml 1N H_2SO_4).

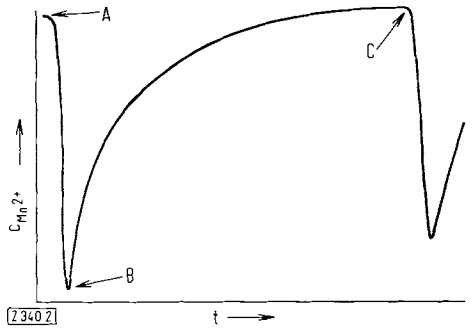


Fig. 2. Typical oscillation period of the bromate-manganese-malic acid oscillator. Mixture: 10ml 10^{-2}M aqueous $MnSO_4$ solution, 20ml 1N H_2SO_4, and 20ml 1M aqueous malic acid solution are mixed. The oscillation starts a little time after addition of 10ml of a 0.25M aqueous bromate solution. Mod. 250, Amp. 1000, H_0 *ca.* 3100 gauss.

We assume that the following reactions take place during a period of oscillation of the bromate – manganese – malic acid oscillator (Fig. 2, A→B→C):

1) A→B: Obviously the concentration of Mn^{2+} ions decreases, for they are oxidized by the bromate to an ESR-inactive oxidation state. The color of the solution (yellow to brown) indicates the presence of Mn^{3+} ions[4]. Reaction (1) probably dominates in this part of the oscillation period.

$$5\ Mn^{2+} + BrO_3^- + 6\ H^+ \rightleftharpoons 5\ Mn^{3+} + 1/2\ Br_2 + 3\ H_2O \quad (1)$$

2) B→C: The concentration of Mn^{2+} increases again, the Mn^{3+} formed by reaction (1) converting the malic acid to oxaloacetic acid in analogy with the oxidation of secondary alcohols[5]. Reaction (2) predominates.

$$2\ Mn^{3+} + HOOCCHOHCH_2COOH \rightleftharpoons 2\ Mn^{2+} + HOOCCOCH_2COOH + 2\ H^+ \quad (2)$$

The oxaloacetic acid formed according to Eq. (2), unlike malic acid, now reacts very rapidly with Br_2.

$$HOOCCOCH_2COOH + Br_2 \rightleftharpoons HOOCCOCHBrCOOH + H^+ + Br^- \quad (3)$$

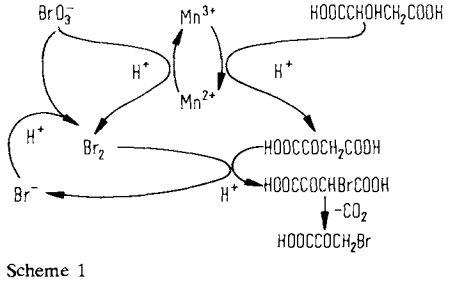
The bromide formed in Eq. (3) is oxidized by bromate to bromine, which once again can undergo reaction according to Eq. (3).

$$BrO_3^- + 5\ Br^- + 6\ H^+ \rightleftharpoons 3\ Br_2 + 3\ H_2O \quad (4)$$

In strong acid medium (> 3N H_2SO_4) vigorous liberation of CO_2 was seen to take place after a short while; we explain this as being due to decarboxylation of the brominated oxaloacetic acid.

$$HOOCCOCHBrCOOH \xrightarrow{-CO_2} HOOCCOCH_2Br \quad (5)$$

The partial reactions (1) to (5) are grouped together in Scheme 1



Scheme 1

In analogous oscillating systems[3c, 3d] bromide occurs as inhibitor. This is also the case in the present system. After addition of bromate the oscillation starts once again. Conversely, the oxidation of Mn^{2+} is renewed by precipitation of the bromide with silver nitrate. After addition of silver nitrate the concentration of Mn^{2+} very rapidly reaches the minimum value. On addition of a larger amount of silver nitrate the corresponding maximum concentration of Mn^{3+} remains constant until the oscillation is renewed with an unchanged period after consumption of the Ag^+ ions.

The occurrence of oscillation in the system under consideration can be explained in the following way: After the components have been added together reactions (1), (2), and (3) start successively, the bromide formed in reaction (3) having an inhibiting effect on reaction (1). A noticeable inhibition of reaction (1) could be achieved at time B in Fig. 2. The Mn^{3+} present at time B is reduced according to Eq. 2 (B→C). The bromide is oxidized according to Eq. 4 to bromine, which once again reacts in Eq. 3, the overall effect corresponding to consumption of bromide. If the concentration of bromide reaches a sufficiently low value, reaction (1) is renewed and a new cycle begins. Thus a negative feedback by bromide ions occurs. As *Higgins*[6] and *Sel'kov*[7] have shown from mathematical models (system of ordinary first order differential equations), oscillations can occur under special conditions in a reaction system where feedback is present.

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Bond Isomerism in Sulfinato Complexes of Transition Metals

By *Ekkehard Lindner, Ingo-Peter Lorenz,* and *Günter Vitzthum*[*]

We were recently able to show that sulfinato complexes are particularly suitable as model compounds for the detection of various phenomena of isomerism[1]. In a study of Fe^{II} complexes of this kind we have now observed the first example of a true bond isomerism of the ambivalent RSO_2^- ligand.

The reaction between $Fe(O_2SR)_2(OH_2)_2$ *(1)*[2] and 2,2'-bipyridine (= bipy) shows a marked dependence on the solvent: In tetrahydrofuran the reactants give exclusively $Fe(O_2SR)_2$bipy *(2)*[3]; in pyridine $Fe(O_2SR)_2(bipy)_2$ *(3)* is obtained; and in water the ionic compound $[Fe(bipy)_3](O_2SR)_2$ *(4)* is formed quantitatively.

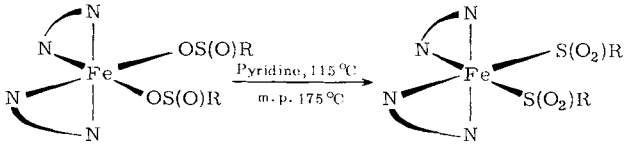
$$(1) \xrightarrow{bipy} (2) \underset{-bipy}{\overset{+bipy}{\rightleftharpoons}} (3) \underset{-bipy}{\overset{+bipy}{\rightleftharpoons}} (4)$$

Sulfinato-*O,O'* Sulfinato-*O,O'* *(a)*, Sulfinato-*O*
(b), Sulfinato-*S*

R = p-$CH_3C_6H_4$

(3) is formed in pyridine at 115 °C as the sulfinato-*S* complex (yield 15%). If *(4)* is treated with boiling, anhydrous acetone under nitrogen in an extraction thimble with sintered disk until the acetone remains colorless (*ca.* 1 h), black-violet $Fe(OS(O)R)_2(bipy)_2$ *(3a)* remains on the disk in 93% yield, while the filtrate contains a 7% yield of the deep red bond isomer $Fe(S(O_2)R)_2(bipy)_2$ *(3b)*. Prolonged extraction results in reversible formation of paramagnetic blue *(2)*.

When heated to 115 °C in pyridine or to its melting point (175 °C), *(3a)* is converted irreversibly into the thermodynamically more stable *(3b)*, m.p. 75 °C.



(3a) *(3b)*

Composition and structure of *(3a)* and *(3b)* can be deduced from elemental analysis and IR and Mössbauer spectra. Evidence for the *O*- and *S*-linkage in these complexes is provided in particular by the position of the SO_2 stretching mode (cf. Table)[4].

Table. SO_2, Fe–O, and Fe–S stretching vibrations (in cm^{-1}) of the complexes *(3a)* and *(3b)*.

(3a)	*(3b)*
1054 vs ν(SO)	1219 vs } $\nu_{as}(SO_2)$
918 vs ν_{as}(SOFe)	1199 vs }
	1034 m } $\nu_s(SO_2)$
	1012 m }
448 m } ν(Fe–O)	368 w-m } ν(Fe–S)
354 m }	290 w-m }

The frequency splitting of ν_{as} and ν_s (SO_2) observed in the case of *(3b)* indicates *cis* bonding of the sulfinato ligand. The Mössbauer spectra show a quintet ground state for *(3a)* (normal magnetic behavior) and a singlet or triplet ground state for *(3b)* (anomalous magnetic behavior). Only a limited number of cases of true bond isomerism were hitherto known, *e.g.* in thio- and seleno-cyanato and nitrito complexes.

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Tungsten Carbide as Anode Material for Fuel Cells

By *Detlef Baresel, Winfried Gellert, Jürgen Heidemeyer*, and *Peter Scharner*[*]

Pohl and co-workers[1] found that tungsten carbide (WC) is an excellent catalyst for the electrochemical oxidation of hydrogen in acid medium. *Sandstede et al.*[2] were able to carry out oxidations of formaldehyde, acetaldehyde, formic acid, hydrazine, and carbon monoxide on WC, but only at low current densities.

Instead of using powdered tungsten metal as starting material for the preparation of WC we used tungsten oxide, which was allowed to react with gaseous carbon-containing compounds, *e.g.* hydrocarbons (C_nH_{2n}, C_nH_{2n+2}) or carbon monoxide (CO). The tungsten oxide which was precipitated from aqueous solution had a large surface area and a high surface activity; it was mixed with powdered oxalic acid, pressed into the desired form, and finally carburized into WC electrodes within 2 to 8 h at temperatures below 750 °C. No support was necessary for the preparation of electrodes having diameters up to 25 mm; however, on increasing the surface area (>10 cm^2) and reducing the thickness (<1mm) the electrodes had to be fitted with a tungsten filament support. For the preparation of permeable electrodes, porous carbon disks were used into which powdered WC (as a suspension in acetone) could be easily deposited. The activity of the electrodes was determined at 70 °C in 3N sulfuric acid in a half cell arrangement by potentiostatic measurement of the current at 300 mV. An autogeneous hydrogen electrode was used as reference point and a carbon rod as counter electrode. The concentration of formaldehyde or formic acid was 6 mole/liter. Hydrogen was passed through the electrode at a pressure of 0.2 at. For all electrodes, the corrosion current (including any possible oxygen-reducing current) was determined in absence of fuel and subtracted from the current measured in the presence of fuel. The differences are quoted as "activity current".

Current densities achieved so far (recorded after 3 hours):

for hydrogen 500 mA/g
for formaldehyde 650 mA/g or 280 mA/cm^2
for formic acid 160 mA/g or 60 mA/cm^2

The current density for hydrogen cannot be quoted in mA/cm^2 because of the electrode construction.

The stationary potentiostatic current-voltage curves for WC electrodes and Raney platinum electrodes of the same size are compared in Fig. 1. It can be seen from the curves that WC is superior to Raney platinum for oxidation of formaldehyde in sulfuric acid in the potential ranges that come into consideration for fuel cell anodes. Appreciable conversion also occurs in the case of formic acid, which can be formed as an intermediate in the oxidation of formaldehyde or methanol.

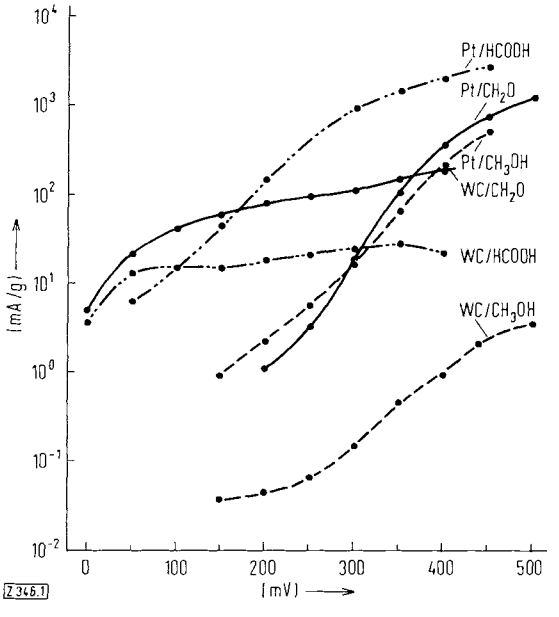


Fig. 1. Electrochemical oxidation of 6M CH_3OH, CH_2O, and HCO_2H on Raney platinum (Pt) and tungsten carbide (WC).

The internal surface areas of the electrodes were between 20 and 30 m^2/g and were determined by a dynamic BET method[3] before and after the electrochemical measurements. The current strengths were considered constant if their values varied by less than 3% over a period of 5 hours.

By using a slightly different technique for the fabrication of electrodes and the same method of preparation of WC much thinner electrodes (*ca.* 0.2 mm) can be prepared having a large surface area and almost the same activity.

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Chromium as Catalyst in Ammonia Synthesis

By *Rudolf Brill, Johannes Kurzidim*, and *Ernst Ruch*[*]

Brill, Richter, and *Ruch*[1] were able to show that a) strong interaction occurs between N_2 and the (111) face of iron, and b) the action of metallic iron as NH_3 catalyst is due to the adsorption of N_2 molecules oriented perpendicular to the (111) face where a weakening of the N≡N bond, arising from overlapping of occupied π orbitals of N_2 with vacant surface orbitals of iron, permits reaction of the molecule with hydrogen. If this concept is correct, other transition metals having the same atomic symmetry and similar interatomic distances as the (111) face of iron should also be catalytically active. These conditions are fulfilled by the (111) face of chromium metal. The correctness of this prognosis has now been confirmed experimentally. The catalyst was prepared by decomposition of dibenzenechromium. Experimental results on a Cr surface of approximately 30 cm^2 are shown in the Table:

Table. NH_3 synthesis: catalyst Cr; T = 436.5 °C.

t	$x \times 10^2$	$k \times 10^3$
0.334	1.63	1.0
0.200	1.38	1.2
0.132	1.01	1.1
0.101	0.87_2	1.1

t = contact time (s); $x = p_{NH_3}/p_{NH_3(\text{equilibrium})}$; k = rate constant.

The rate constants of NH_3 formation for a given surface area are of the same order of magnitude as for iron. This confirms the mechanism of NH_3 synthesis derived from another series of experiments[2], according to which the initial product is N_2H; further hydrogenation and eventual dissociation yields NH_3.

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Generalization of the Isosbestic Point

By *Ch. Chylewski*[*]

A simple graphical representation of spectrophotometric data permits similar conclusions to be drawn as the occurrence of isosbestic points while allowing freedom of choice of the wavelength.

The widespread view that the occurrence of isosbestic points (points of constant extinction) in families of absorption spectra proves the presence of only two absorbing components in the chemical system under study is erroneous[1]. *Schläfer* and *Kling*[2] have demonstrated the correct conditions: Isosbestic points indicate that the changes in concentration of all absorbing components are related *linearly* when one parameter such as pH, time, or temperature is varied. The linearity follows from the stoichiometry if the concentrations of all absorbing components are connected by a *single* reaction equation. Kinetically this means that the reaction has only *one* rate-determining step and the respective rate law can be expressed as a single first-order differential equation. Isosbestic points provide no information about the number of participating substances. Further reasoning assumes the validity of Beer's law. Moreover, all absorbing substances should exhibit linearly independent spectra, a condition that is not always satisfied in practice.

The wavelengths at which isosbestic points occur, if at all, depend upon the absorption spectra of the participating substances and are not known in advance in the case of a new reaction. They are therefore found by recording the absorption spectra over a whole range of wavelengths in the hope that at least one of the points sought is found within this interval. This restricts the application of the method to the study of slow reactions. In addition, isosbestic points sometimes lie in spectral regions in which measurements are inaccurate or even impossible with the equipment available, or in which traces of impurities or side reactions have a pronounced effect. Finally there is still a general lack of equipment for the direct superposition of spectra in such a manner that the isosbestic points are readily recognized; copying operations lead to a loss in accuracy and waste time.

To prove: The extinction of a system is measured at two wavelengths λ_1 and λ_2 and the measured values plotted against each other in a system of Cartesian coordinates. There results a point whose position depends upon the concentrations of all components absorbing at these wavelengths. If a parameter that affects the concentrations is varied continuously, this point moves on a *straight line* under the same condition for which isosbestic points occur.

Proof: The reaction equation is taken to be:

$$a_1A_1 + a_2A_2 + \ldots \rightarrow a_iA_i + a_{i+1}A_{i+1} + \ldots \quad (1)$$

where a_i are stoichiometric reaction coefficients, A_i are the species participating in the reaction (the subscript has a mathematical rather than a chemical significance). The concentration of species A_i is c_i, and the initial concentration is c_i^0. If the coefficients on the left hand side of equation (1) are regarded as being negative and a reaction variable X is introduced[3], the following equation applies throughout the reaction:

$$c_i = c_i^0 + a_iX \quad (2)$$

ε_i is the extinction coefficient for species A_i as measured for a sample of 1 cm thickness. If Beer's law is valid, the extinction of the whole system at any wavelength is given by

$$E = \sum_i \varepsilon_i c_i = \sum_i \varepsilon_i c_i^0 + X \sum_i \varepsilon_i a_i \qquad (3)$$

Substances whose concentration remains constant throughout the reaction (*e.g.* the solvent) can be accounted for formally by assignment of a reaction coefficient of zero.

E and ε_i depend upon the wavelength. They have the values E_1 and $\varepsilon_{i,1}$ and E_2 and $\varepsilon_{i,2}$ at the wavelengths λ_1 and λ_2 respectively:

$$\begin{aligned} E_1 &= \sum_i \varepsilon_{i,1} c_i^0 + X \sum_i \varepsilon_{i,1} a_i \\ E_2 &= \sum_i \varepsilon_{i,2} c_i^0 + X \sum_i \varepsilon_{i,2} a_i \end{aligned} \qquad (4)$$

Eq. (4) is the parametric representation of a straight line from which X can be eliminated:

$$E_1 = \frac{(E_2 - \sum_i \varepsilon_{i,2} c_i^0) \sum_i \varepsilon_{i,1} a_i}{\sum_i \varepsilon_{i,2} a_i} + \sum_i \varepsilon_{i,1} c_i^0 \qquad (5)$$

Thus it is established that E_1 and E_2 are connected by a linear relation.

In practice the converse of this proof is more important, *i.e.* deduction of the number of reaction variables from the linearity of the observed function. The converse applies when the slope of the line is negative. Provided that the spectra are continuous, this slope is a continuous function of λ_1 and λ_2. If, *e.g.*, λ_1 approaches λ_2, the slope assumes all values between a negative amount and one, and must therefore be zero at one wavelength at least. However, a straight line of zero slope corresponds to an isosbestic point whose existence is thus proved indirectly.

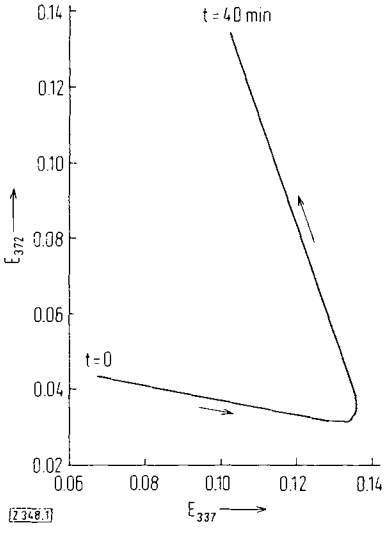


Fig. Example of a reaction that proceeds in two stages, each having one rate-determining reaction step (reduction of methyl orange by 1,2-dihydro-2,3-dimethylquinoxaline in excess at pH 0).

If the line observed has a positive slope, this suggests, but does not prove, that the reaction has only one reaction variable. The line is particularly uninformative if its extrapolation passes close to or through the origin. In such a case it is highly probable that it is mainly the same species that is absorbing at both the wavelengths chosen. A straight line then clearly results purely on the basis of Beer's law, independently of the stoichiometry of the reaction.

Measuring technique and applications: When the parameter to be varied is not the time, the successive measurement at two wavelengths gives rise to no difficulties. On the other hand, four possible methods are available for a kinetic study:

a) Simultaneous extinction measurements at two wavelengths. Suitable spectrophotometers are commercially available.

b) Alternate measurements at two wavelengths with interpolation of the missing values. This method has proved very effective in our laboratory. About 10 alternations are sufficient for the half-life of a reaction. With a Beckman DB–G instrument it is possible to switch over once every second provided that the two wavelengths are not too far apart. The interpolation can be carried out graphically or numerically.

c) Stopping the reaction. This method is of greatest interest for photochemical reactions where samples can be taken at regular intervals from the irradiation vessel, the reaction being interrupted in the samples themselves.

d) Repetition of the reaction. The extinction is first measured at one wavelength, and then at a second wavelength for a reaction mixture that is as similar as possible to the first. This is not recommended in the case of slow reactions since kinetic data are often not very accurately reproducible and poorer results are obtained than with method b) for double the experimental effort. We have successfully employed the technique for fast reactions which can be reproduced several times in a short period and for which it is impossible to switch over the monochromator.

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[1] *G. Kortüm:* Kolorimetrie, Photometrie und Spektrometrie. Springer, Berlin 1962, p. 32.

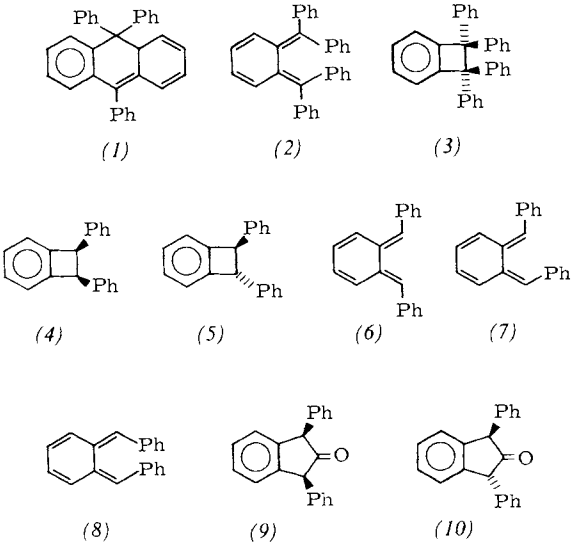
[2] *H. L. Schläfer* and *O. Kling*, Angew. Chem. *68*, 667 (1956)

[3] X has the dimensions of a concentration.

Kinetic Spectrophotometry of Relaxation Systems Containing 7,8-Polyphenyl-Substituted *o*-Quinodimethane Derivatives[1]

By *Karl-Heinz Grellmann, Joachim Palmowski,* and *Gerhard Quinkert*[*]

o-Quinodimethanes have only a young history as experimentally confirmed intermediates. Kinetic[2] and stereochemical[3] investigations require, and low temperature ($< -180\,°C$) electronic spectra[4,5] establish, their part as kinetically unstable seco isomers of benzocyclobutenes of the appropriate constitution and configuration. Results of flash photolysis experiments at temperatures between -53 and $23\,°C$[6] provide information about other modes of formation, lifetimes, and reactions of these species.



(1) (2) (3) (4) (5) (6) (7) (8) (9) (10)

Thermal cyclization of 7,7,8,8-tetraphenyl-*o*-quinodimethane affords, depending on the temperature used, the cyclo isomers *(1)* or *(3)*, which have been interpreted as being the thermodynamically or kinetically determined products, respectively[4]. Flash photolysis of *(1)* and *(3)* (Fig. 1) reveals the presence of the common intermediate *(2)*; *(2)* rapidly cyclizes to *(3)* [$\tau = 3.6 \times 10^{-5}$ s at 23 °C; Arrhenius activation parameters: E = 15.3 kcal/mole, $A = 3.2 \times 10^{15}$ s^{-1} (measured between −53 and 23 °C)], while the formation of *(1)* from *(3)* is relatively slow.

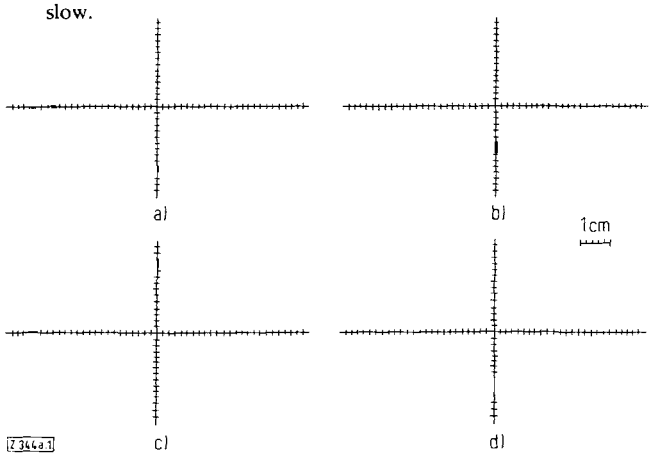


Fig. 1. Oscilloscopic traces after flashing a 1.66×10^{-5} M solution of *(1)* in methylcyclohexane [7a].

a) (T = 23 °C; t = 0.5 ms/cm; λ = 450 nm; S = 1.0 V/cm): The primary product *(2)* formed by light-induced cyclo/seco isomerization, which, unlike the reactant *(1)* absorbs at 450 nm [4], decays in a thermally induced first order seco/cyclo isomerization to give the secondary product *(3)* ($k_{(2)\rightarrow(3)} = 2.8 \times 10^4 s^{-1}$) which does not absorb above 300 nm [4].

b) (T = 23 °C, t = 0.05 ms/cm; λ = 400 nm; S = 5.0 V/cm): Light induced cyclo/seco isomerization of the reactant *(1)* leads to the primary product *(2)* which absorbs weaker at 400 nm and which undergoes a thermally induced first-order seco/cyclo isomerization to give *(3)* ($k_{(2)\rightarrow(3)} = 2.8 \times 10^4$ s^{-1}).

c) (T = 23 °C, t = 1000 ms/cm; λ = 400 nm, S = 0.5 V/cm): The secondary product *(3)* is completely reconverted in a two-stage first order reaction *via (2)* into the original reactant *(1)*; $k_{(3)\rightarrow(1)} = 0.385$ s^{-1}.

d) (T = −35 °C; t = ms/cm; λ = 400 nm; S = 0.5 V/cm): Compound *(3)* prepared from *(1)* by irradiation is kinetically unstable at room temperature [4] and is converted in a light-induced cyclo/seco isomerization into *(2)* which absorbs at 400 nm and shows the same spectral data [7b] as the primary product formed from *(1)* by light-induced cyclo/seco isomerization, and which regenerates *(3)* in a thermally induced first-order seco/cyclo isomerization ($k_{(2)\rightarrow(3)} = 57$ s^{-1}).

According to their electronic absorption spectra the light-induced ring opening of the configurationally isomeric benzocyclobutene derivatives *(4)* and *(5)* (with 254-nm light) at −189 °C proceeds non-stereospecifically, although stereoselectively[5]. All three configurationally isomeric *o*-quinodimethane derivatives *(6)*, *(7)*, and *(8)* participate in the reaction[8]; their relative proportions depend on the viscosity of the medium. Flash photolysis of *(4)* and *(5)* at 21.6 °C (Fig. 2) reveals three distinct decay processes. A comparison of the absorption spectra of those *o*-quinodimethanes[9] obtained either directly using low-temperature techniques at −186 °C or by point by point scanning at 21.6 °C using kinetic spectrophotometry indicates that *(6)* (τ = 19 ms; E = 15 kcal/mole) and *(7)* (τ = 690 ms; E = 17 kcal/mole) cyclize to the benzocyclobutenes *(5)* and *(4)*[5] in order of their decreasing rates; at 21.6 °C *(6)* and *(7)* are formed from *(4)* or *(5)* in 13 and 87% or 26 and 74% yield, respectively[10].

Electronic spectroscopic control experiments show[13] that the *o*-quinodimethane derivatives *(6)* and *(7)* also occur in the photodecarbonylation of the configurationally isomeric 2-indanone derivatives *(9)* and *(10)*[12] at −189 °C. According to flash photolysis experiments, the same is true for the light-induced CO elimination at 21.6 °C; *(6)* and *(7)* are formed from *(9)* or *(10)* in the ratios of 54:46 or 47:53 respectively[10] (Fig. 3).

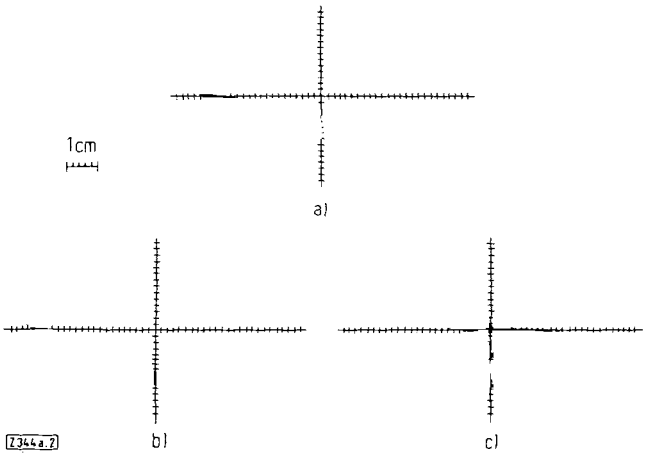


Fig. 2. Oscilloscope traces after flashing a 2.67×10^{-4} M solution of *(5)* in methylcyclohexane at 21.6 °C [7a].

a) (t = 10 ms/cm; λ = 440 nm; S = 1.0 V/cm): Light-induced cyclo/seco isomerization of *(5)* [11a] leads to formation of *(6)* which rapidly undergoes first order decay (k = 52.5 s^{-1}) [11b].

b) (t = 500 ms/cm; λ = 440 nm, S ≈ 0.5 V/cm): Compound *(7)*, which also decays with first order reaction kinetics, but slower (k = 1.5 s^{-1}) than *(6)*, is also formed [11b].

c) (t = 500 ms/cm; λ = 250 nm; S ≈ 0.5 V/cm): A third decay process of minor importance takes place which again proceeds *via* a first order reaction: the species formed, which cannot be detected by flash spectroscopy, has a halflife of about 20 s.

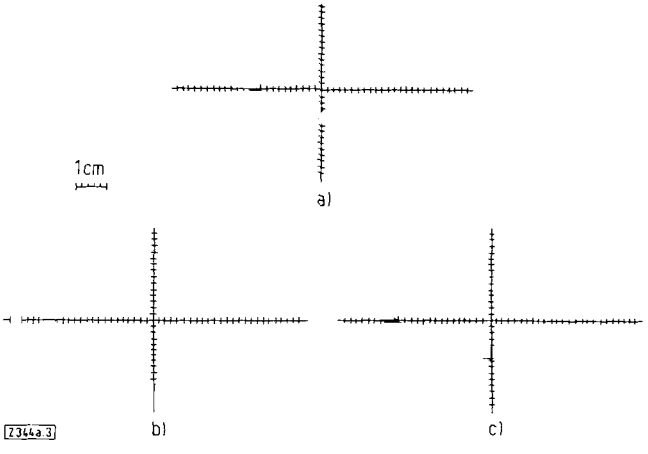


Fig. 3. Oscilloscope traces after flashing a 2.44×10^{-4} M solution of *(10)* (a and b) and a 3.49×10^{-4} M solution of *(9)* (c) in methylcyclohexane at 21.6 °C [7a].

a) (t = 10 ms/cm; λ = 440 nm; S = 0.5 V/cm): Decay curve (first order) of *(6)* formed from *(10)* by photodecarbonylation (k = 52.5 s^{-1}; E = 15 kcal/mole; λ_{max} = 450 nm).

b) (t = 500 ms/cm, λ = 440 nm; S = 0.2 V/cm): First order decay of *(7)* which is formed in practically the same amount as *(6)* (k = 1.5 s^{-1}; E = 17 kcal/mole; λ_{max} = 445 nm).

c) (t = 10 ms/cm; λ = 440 nm; S = 1.0 V/cm): First order decay of *(6)* formed from *(9)* by photodecarbonylation (k = 52.5 s^{-1}; E = 15 kcal/mole; λ_{max} = 450 nm) [14].

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[1] This work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

[2] *R. Huisgen* and *H. Seidel*, Tetrahedron Lett. *1964*, 3381.

[3] *G. Quinkert, K. Opitz, W.-W. Wiersdorff*, and *M. Finke*, Tetrahedron Lett. *1965*, 3009; Liebigs Ann. Chem. *693*, 44 (1966).

[4] *G. Quinkert, W.-W. Wiersdorff, M. Finke, K. Opitz*, and *F.-G. von der Haar*, Chem. Ber. *101*, 2302 (1968).

[5] *G. Quinkert, M. Finke, J. Palmowski*, and *W.-W. Wiersdorff*, Mol. Photochem. *1*, 433 (1969).

[6] Performance and evaluation see *K. H. Grellmann, E. Heilbronner, P. Seiler*, and *A. Weller*, J. Amer. Chem. Soc. *90*, 4238 (1968).

[7a] The first portion of the curve shows the position of the base line, upward (downward) deviations correspond to a decrease (increase) in the transparency. T = temperature; t = sweep rate of trace; λ = wavelength at which decay curve was recorded; S = sensitivity (V_0 = 10 V); $\tau = 1/k$. – The time-dependent photomultiplier signals V_0 (before flashing) and $V = V_t$ (at time t after flashing) are proportional to the intensity I of the signal. The change in optical density $\Delta E = \Delta E(t)$ is $\Delta E(t) = \log I_0/I_t = \log V_0/V_t$.

[7b] Low-temperature spectroscopic data [4]: λ_{max} (ε) = 284 (30600) and 519 nm (9170), $\varepsilon_{284}/\varepsilon_{519} = 3.34$; flash spectroscopic data of relative intensity: λ_{max} = 290 and 505 nm, $\varepsilon_{290}/\varepsilon_{505} = 3.3$.

[8] See footnote 14 in [5].

[9] The photo product obtained from *(4)* at −189 °C [5] has an absorption maximum at 465 nm (ε = 10600); warming to −178 °C results in an irreversible shift of the maximum to 455 nm without change in intensity. This observation concerns that portion of the *o*-quinodimethane derivatives able to photocyclize and is compatible with a *Z/E* isomerization of *(8)* to *(7)*.

[10] The quantitative results are based on the observation that the absorption of *(6)* at 455 nm has almost twice the intensity (20100) of that of the other configurational isomers.

[11a] The flash photolysis of *(4)* shows – apart from a slight participation of *(6)* – analogous behavior.

[11b] According to low-temperature spectroscopic (flash spectroscopic) data recorded in methylcyclohexane/3-methylpentane, 4:1 (methylcyclohexane), the long wavelength absorption maximum of the thermally most labile *o*-quinodimethane derivative *(6)* unable to photocyclize [5] appears at 455 nm [9] (450 nm at 21.6 °C); *(7)* shows a maximum at 455 (445) nm.

[12] *G. Quinkert, H.-P. Lorenz*, and *W.-W. Wiersdorff*, Chem. Ber. *102*, 1597 (1969).

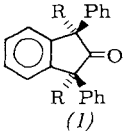
[13] *G. Quinkert, J. Palmowski, H.-P. Lorenz, W.-W. Wiersdorff*, and *M. Finke*, Angew. Chem. *83*, 210 (1971); Angew. Chem. internat. Edit. *10*, 198 (1971).

[14] In this case compound *(7)*, which occurs in the same way, was determined only flash spectroscopically (λ_{max} = 450 nm).

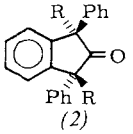
Non-Cheletropic Photodecarbonylation of 1,3-Diphenyl-Substituted 2-Indanone Derivatives[1]

By *Gerhard Quinkert, Joachim Palmowski, Hans-Peter Lorenz, Walter-Wielant Wiersdorff*, and *Manfred Finke*[*]

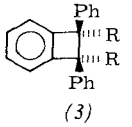
Unconjugated cyclopentenones undergo smooth decarbonylation, both in their electronic ground state[2] and after $\pi^* \leftarrow n$ excitation[3] to give butadiene derivatives. If the thermal decarbonylation proceeds in one step, the correlation diagrams demand a stereospecific, in the present case disrotatory, course[2b,4]. The stereochemistry of the corresponding photodecarbonylation, which has been discussed under different, in part contradictory, premises, is *a priori* unclear. Two shortcomings are responsible for this, *viz.* insufficient knowledge of the photoreactive state and lack of a conclusive theory of light-induced reactions.



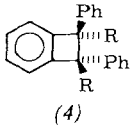
(1)



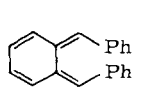
(2)



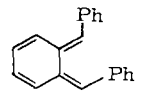
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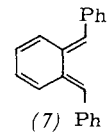
(4)



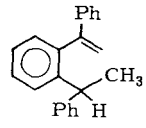
(5)



(6)



(7)



(8)

(a), R = H
(b), R = CH_3
(c), R = D

Photodecarbonylation of the symmetric 2-indanone derivatives *(1a)* and *(2a)*[5] in hydrocarbon mixtures at −189 °C with 313-nm light affords the 7,8-diphenyl-substituted *o*-quinodimethanes, *(5)*, *(6)*, and *(7)*, which, on the basis of their absorption spectroscopic properties have already been differentiated as photocyclizable [*(5)* and *(6)*] and non-photocyclizable *(7)* configurations[6]; the *o*-quinodimethane derivative *(7)* unable to photocyclize is formed from *(1a)* in 61.5% yield and from *(2a)* in 95% yield.

A stepwise monitoring of the reaction showed that the ratio of the two configurational types [*(5)* + *(6)* and *(7)*] formed from *(2a)* is independent of the progress of the reaction, whereas the composition of the product in the case of *(1a)* is a function of the irradiation time since a photostereomutation of the educt[7] takes place. In the latter case, extrapolation to zero time (t=0) shows that the initial products formed are almost exclusively *o*-quinodimethanes having the photocyclizable configuration. However, since no information is available as to whether *(5)* and/or *(6)* is initially formed from *(1a)*[8], a quantitative determination of the two configurational types in light-induced low-temperature decarbonylation does not afford conclusive details about the (one- or multi step) course of the reaction.

Table. Data of the decarbonylation of *(1a)*, *(1b)*, *(2a)*, and *(2b)* at 13±2 °C in ether with 313-nm light.

Educt	Conversion (%)	Hydrocarbon fraction [a] Ratio of isomers (%)	Ketone fraction [a] Ratio of isomers (%)
(1a)	50	*(3a)*: 8; *(4a)*: 92	*(1a)*: 87; *(2a)*: 13
	67	*(3a)*: 10; *(4a)*: 90	*(1a)*: 58; *(2a)* 42
	80	*(3a)*: 11; *(5a)*: 89	*(1a)*: 36; *(2a)* 64
(2a)	36	*(3a)*: 18; *(4a)*: 82	
	48	*(3a)*: 17; *(4a)*: 83	exclusively *(2a)*
	70	*(3a)*: 13; *(4a)*: 87	
(1b)	30	*(3b)*: 69; *(4b)*: 31	
	53	*(3b)*: 70; *(4b)*: 30	exclusively *(1b)*
	66	*(3b)*: 69; *(4b)*: 31	
	100 [b]	*(3b)*: 29; *(4b)*: 12; *(8)*: 59	
(2b)	25	*(3b)*: 8; *(4b)*: 92	
	41	*(3b)*: 10; *(4b)*: 90	exclusively *(2b)*
	50	*(3b)*: 9; *(4b)*: 91	
	100 [b]	*(3b)*: 1; *(4b)*: 67; *(8)*: 32	

[a] The irradiation products were analyzed by gas chromatography [5] and by NMR spectroscopy [12] after treatment with an excess of $LiAlH_4$ and chromatographic separation of the alcohols from the hydrocarbons; the presence of piperylene (0.75 M) showed no effect on the conversion and the product composition.

[b] Irradiation at −78 °C.

The Table contains data of the decarbonylation of *(1a)*, *(1b)*, *(a)*, and *(2b)*[5] in a merry-go-round apparatus[9]. In each case a mixture of configurational isomers of four-membered ring hydrocarbons *(3)* and *(4)* occur, the composition of which remains unaffected by the presence of the ketone triplet quencher piperylene. Simulation of a trivial non-stereospecificity by photostereomutation of the benzocyclobutene derivatives does not occur in direct irradiation or sensitization[10]; in contrast to *(1a)* a light-induced configurational isomerization of the ketonic reactants *(1b)*, *(2a)*, and *(2b)* does not come into consideration. Although it has been established, for example, that *(3a)*

and *(4a)* are formed stereospecifically[12] from the corresponding seco isomers also detected at room temperature[11], a thermal and/or photo configurational isomerization of the intermediate compounds under these conditions cannot be ruled out. The observed non-stereospecificity is therefore irrelevant for the course of the reaction in question. However, the fact that photostereomutation and photodecarbonylation in *(1a)* result from one and the same electronically excited singlet state verifies the stepwise, noncheletropic character of the light-induced CO elimination in the case of the cyclopent-3-en-1-one system investigated[13].

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[1] This work was supported by Farbwerke HoechstAG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

[2] a) *C. F. H. Allen,* Chem. Rev. *37,* 209 (1945); *62,* 653 (1962); b) *J. E. Baldwin,* Can. J. Chem. *44,* 2051 (1966).

[3] a) *L. D. Hess* and *J. N. Pitts, jr.,* J. Amer. Chem. Soc. *89,* 1973 (1967); b) *G. Quinkert, K. Opitz, W.-W. Wiersdorff,* and *J. Weinlich,* Tetrahedron Lett. *1963,* 1863; c) *B. Fuchs,* Israel J. Chem. *6,* 511, 517 (1968); J. Chem. Soc. *C 1968,* 68.

[4] a) *R. B. Woodward* and *R. Hoffmann,* Angew. Chem. *81,* 797 (1969); Angew. Chem. internat. Edit. *8,* 781 (1969); Science *167,* 825 (1970); b) *D. M. Lemal* and *S. D. McGregor,* J. Amer. Chem. Soc. *88,* 1335 (1966); c) *H.-P. Lorenz,* Dissertation, Technische Universität Braunschweig 1968.

[5] *G. Quinkert, H.-P. Lorenz,* and *W.-W. Wiersdorff,* Chem. Ber. *102,* 1517 (1969).

[6] *G. Quinkert, M. Finke, J. Palmowski,* and *W.-W. Wiersdorff,* Mol. Photochem. *1,* 433 (1969).

[7] For the analysis of the irradiation product regarding photocyclizable and non-photocyclizable *o*-quinodimethane derivatives see [6].

[8] See footnote 14 in Ref. [6].

[9] *B. Bronstert,* Diplomarbeit, Technische Universität Braunschweig 1968.

[10] Irradiation of mixtures of *(1c)* and *(3a)* or of *(1c)* and *(4a)* with 313-nm light does not result in stereomutation of the hydrocarbons used.

[11] *K. H. Grellmann, J. Palmowski,* and *G. Quinkert,* Angew. Chem. *83,* 209 (1971); Angew. Chem. internat. Edit. *10,* 196 (1971).

[12] *G. Quinkert, K. Opitz, W.-W. Wiersdorff* and *M. Finke,* Liebigs Ann. Chem. *639,* 44 (1966).

[13] Premise for positive conclusions from quencher experiments: If the energy hypersurface contains several triplet conformations they all must be quenchable.

Increase in Selectivity of Photoelimination Products on Replacing the Liquid Phase by the Crystalline Phase[1]

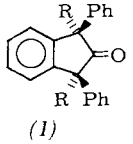
By *Gerhard Quinkert, Takao Tabata, Eckhard A. J. Hickmann,* and *Walter Dobrat*[*]

The observation that photodecarbonylation of 1,3-diphenyl substituted 2-indanone derivatives[2] does not take place in a single step[3] indicates an intermediacy of biradicals, which, because of internal rotations and inversion at radical centers comprise whole groups of subspecies. Experience has shown that in such cases the preparatively as well as mechanistically useful product selectivity increases with increasing viscosity of the medium[4]. The crystal lattice of a solid is expected to have a particularly strong influence on the rate, and possibly the direction, of molecular motion. Investigations carried out at the Weizmann Institute[5,6] suggest that the crystalline phase is a suitable medium for photoeliminations as it allows entry of light and escape of gaseous products.

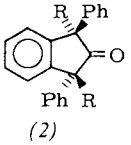
A considerable increase of the cage effect, and consequently of the constitutional selectivity, is observed for the photodecarbonylation of 1,1,3-triphenyl-2-propanone[2a] by substituting the crystalline phase for the (benzene) solution. The extent of the cage effect given by the ratio:

$$a = \frac{^{2M}[1,1,2\text{-triphenylethane}]}{^{M}[\text{reactant}]} - 1;\ M = \text{mole equivalent.}$$

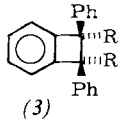
increases from the one limiting value $a = 0$ in solution (1,2-diphenylethane, 1,1,2-triphenylethane, and 1,1,2,2-tetraphenylethane occur in the ratio 1:2:1[2a]) to the other limiting value $a = 1$ in the solid (1,1,2-triphenylethane is formed exclusively). The constitutional selectivity for the photodenitrogenation of diphenylmethylazotoluene changes less drastically; practically only 1,1,2-triphenylethane occurs in the light-induced N_2 elimination in the crystalline phase at −196 °C[7], while on irradiation of a benzene solution at 27 °C *a* falls only to 0.28[8]. This finding is in accordance with the higher kinetic stability of an acyl radical relative to the isoelectronic diazoalkyl radical[9].



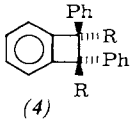
(1)



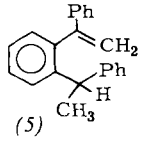
(2)



(3)



(4)



(5)

(a), R = H
(b), R = CH_3
(c), R = D

Table. Data of the decarbonylation of *(1a), (1b), (2a),* and *(2b)* in solution and in the crystalline phase.

Reactant \ Product	Percentage composition in	
	Solution [a]	Cryst. phase [b]
(1a)	*(3a)*: 11 *(4a)*: 89	*(3a)*: 95 *(4a)*: 5
(2a)	*(3a)*: 13 *(4a)*: 87	*(3a)*: 5 *(4a)*: 95
(1b)	*(3b)*: 69 *(4b)*: 31	*(3b)*: 90 *(4b)*: 4 *(5)*: 6
(2b)	*(3b)*: 9 *(4b)*: 91	*(3b)*: 14 *(4b)*: 86

[a] The products obtained by irradiation of an ethereal solution at 13 ± 2 °C with 313-nm light were analyzed by gas chromatography [12] and by NMR spectroscopy [2b] after treatment with an excess of $LiAlH_4$ and subsequent chromatographic separation of the alcohols from the hydrocarbons.

[b] Irradiation was carried out in a Rayonet reactor (300-nm lamp; Southern Ultraviolet Co., Middleton, Conn.) using a filter (2.5% aqueous solution of potassium hydrogen phthalate; layer thickness 8 mm) in a Duran vessel of wall-thickness 1 mm at 13 ± 2 °C. For a detailed analysis of the irradiation products see [a]; in none of the cases was a stereomutation of the educt observed.

As a result of the restricted internal mobility of the intermediate species formed from the configurationally isomeric ketone pairs *(1a)/(2a)* and *(1b)/(2b)*[12] on UV irradiation, the configurational selectivity of the subsequently isolated benzocyclobutene derivatives *(3)* and *(4)* increases considerably on changing from the solution to the crystalline phase as a reaction system and in one case even changes its direction.

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German version: Angew. Chem. *83*, 212 (1970)

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[1] This work was supported by Farbwerke Hoechst AG, the Deutsche Forschungsgemeinschaft, and the Fonds der Chemischen Industrie.

[2] a) *G. Quinkert, K. Opitz, W.-W. Wiersdorff,* and *J. Weinlich,* Tetrahedron Lett. *1963*, 1863; b) *G. Quinkert, K. Opitz, W.-W. Wiersdorff,* and *M. Finke,* Liebigs Ann. Chem. *693*, 44 (1966); c) *G. Quinkert, W.-W. Wiersdorff, M. Finke, K. Opitz,* and *F.-G. von der Haar,* Chem. Ber. *111*, 2302 (1968).

[3] *G. Quinkert, J. Palmowski, H.-P. Lorenz, W.-W. Wiersdorff,* and *M. Finke,* Angew. Chem. *83*, 210 (1971); Angew. Chem. internat. Edit. *10*, 198 (1971).

[4] *P. D. Bartlett* and *J. M. McBride,* Pure Appl. Chem. *15*, 89 (1967).

[5] *G. M. J. Schmidt* in: Proceedings of the Thirteenth Conference on Chemistry at the University of Brussels, October 1965; Reactivity of the Photoexcited Organic Molecule. Interscience Publ., New York 1967.

[6] *M. D. Cohen,* Pure Appl. Chem. *9*, 567 (1964).

[7] Low temperatures were chosen in order to guarantee the crystalline character of the irradiated sample; at −26 °C an additional compound was formed (4%) which was not further investigated.

[8] a) No cage effect is observed to take place in the thermolysis of diphenylmethylazotoluene at 120 °C, either in the melt or in benzene solution. b) The result of a nuclear spin polarization investigation by *G. L. Closs* and *A. D. Trifunac* [J. Amer. Chem. Soc. *91*, 4554 (1969)] indicates a factor $a = 0.2$.

[9] Stepwise decarbonylation is typical even for constitutionally symmetrical ketones [10]; stepwise denitrogenation has been detected only occasionally in the case of constitutionally asymmetrical azo compounds [11].

[10] *W. K. Robins* and *R. H. Eastman,* J. Amer. Chem. Soc. *92*, 6077 (1970).

[11] *S. Seltzer* and *F. T. Dunne,* J. Amer. Chem. Soc. *87*, 2628 (1965).

[12] *G. Quinkert, H.-P. Lorenz,* and *W.-W. Wiersdorff,* Chem. Ber. *102*, 1517 (1969).

CONFERENCE REPORTS

Present Trends in Polyurethane Chemistry

By *Helmut Piechota*[*]

The discovery of the diisocyanate polyaddition process for the production of macromolecular materials has led to a wide variety of valuable synthetic materials within a little more than 30 years: PUR elastomers, which can be cast or sprayed or, alternatively, injection molded or extruded, are commonly encountered nowadays. The same applies to urethane lacquers and varnishes, to PUR coatings for fabrics, to PUR synthetic leather, to adhesives, and to PUR synthetic fibers and foams. (PUR has become an accepted abbreviation for polyurethane.)

The production of PUR raw materials (polyisocyanates, polyethers, polyesters), which is nowadays carried out on a full industrial scale, requires an accurate knowledge of the structural parameters that determine the properties of the resulting polyurethane. The starting materials are made to react in one step or by the prepolymer process under strictly controlled conditions to give polyurethane. By suitable choice of raw materials and control of the reaction it is possible to determine the properties of the PUR product in advance: polyurethanes are "tailor made" plastics.

The most important PUR products are foams, which can be produced in all degrees of hardness. In 1970 world production exceeded 10^6 tons. Flexible PUR foams in the form of continuously produced slabs or foamed in place are used as upholstering materials, for mattresses, automobile seats, *etc.* Recent developments include foams that are self-extinguishing under defined test conditions, as well as "cold foams". The latter are used in the manufacture of molded materials having properties resembling those of latex foams. They have been rapidly accepted, *e.g.* for the production of automobile seats and arm chairs.

Rigid PUR foams are excellent insulating materials. Practically all European household refrigerators are insulated with such materials, as are also refrigerated vehicles, cold stores, district heating supply pipes, flat roofs of buildings, *etc.* In the future, the sandwich technique, *i.e.* the combination of rigid facings with a core of rigid PUR foam, will become increasingly important and many examples of its industrial application can already be given. Increasing use in building construction raises the question of fire prevention: Recent developments have resulted in the trimerization of polymeric diphenylmethane diisocyanate with simultaneous foaming. The polyisocyanurate foams thus produced are flame retardant and comply with the German industrial standard DIN 4102.

PUR structural foams are produced by foaming in place. By taking particular chemical and process-engineering measures it is possible to produce, from a single reaction mixture in a one-step operation, a molded article having a massive skin, which is gradually transformed towards the microporous core. Soft and semirigid structural PUR foams are widely used for automobile safety fittings (*e. g.* arm rests, crash pads, bumpers) and also for lightweight shoe soles that can be foamed directly onto the shoe shaft. Owing to their sandwich structure, rigid PUR structural foams represent novel materials of construction that are suitable for the production of large-surface, high-volume moldings. These materials have acquired an important position in the furniture industry, in the manufacture of casings, and in the sports equipment industry.

There is probably no other field in the plastics industry where chemistry and process engineering are so closely linked as in the polyurethanes. From the chemical point of view increasing attention is being devoted to other reactions of the isocyanate group (*e. g.* trimerization), while in process engineering new molding techniques are being sought (*e. g.* structural foams). This leads to new materials with novel properties for new applications (*e. g.* agricultural foams). 30 years of PUR chemistry clearly represents not a final goal but a milestone on the way of continuing progress.

Lecture at Dortmund on December 15, 1970 [VB 266 IE]
German version: Angew. Chem. *83*, 179 (1971)

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Continuous Emulsion Polymerization

By *Heinz Gerrens*[*]

Several industrially important plastics such as butadiene-styrene rubbers and emulsion polyvinyl chloride are nowadays prepared by continuous emulsion polymerization. A trend towards increasing use of continuous processes can also be expected to parallel increased production in the case of plastic dispersions. The properties of the plastics, and particularly those of the dispersions, strongly depend on the process variables; consequently, a knowledge of the relevant reaction kinetics is most important on changing from batch to continuous processes.

The continuous emulsion polymerization of styrene and of methyl acrylate in a series of three continuous stirred tank reactors has been investigated[1]. The number of particles and over-all reaction rate were measured as a function of the emulsifier and initiator concentration, mean residence time, and temperature. The results obtained with styrene are in fairly good agreement with the theory proposed by *Gershberg* and *Longfield*[2]. Deviations from theory in the case of methyl acrylate can be qualitatively explained by the relatively high solubility of this monomer in water, which favors direct particle formation from the aqueous phase and transfer of radicals from one latex particle to another.

According to a theory put forward by *Matsuura* and *Kato*[3] one unstable and two stable stationary operating states can occur in an isothermally and continuously operating ideal stirred tank reactor if the reaction under investigation has autocatalytic character. Under certain conditions, a high self-acceleration due to the Trommsdorff effect is apparent in the emulsion polymerization of styrene. In continuous reactions carried out in the three-stage series of stirred tank reactors, six stable stationary operating points were found for the individual reactors and three stable operating states for the whole series[4]. The data obtained were in good agreement with the values expected theoretically from a time-conversion plot of the batch process. A changeover from one stable operating point to another in one of the reactors occurs if the monomer concentration is suddenly increased for a short time. Theoretically, in a series of n reactors a maximum of $n+n(n+1)/2$ stable and n unstable stationary operating points are possible in the individual reactors and $n+1$ stable operating states in the whole series.

Lecture at Karlsruhe, November 19, 1970 [VB 263 IE]
German version: Angew. Chem. *83*, 151 (1971)

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[1] *H. Gerrens* and *K. Kuchner*, Brit. Polymer J. *2*, 18 (1970).

[2] *D. B. Gershberg* and *J. E. Longfield*, Symp. Polymerization Kinetics Catalyst Systems, Part I; 54th Meeting, A. I. Ch. E., New York, Dec. 2–7, 1961, Preprint 10.

[3] *T. Matsuura* and *M. Kato*, Chem. Eng. Sci. *22*, 171 (1967).

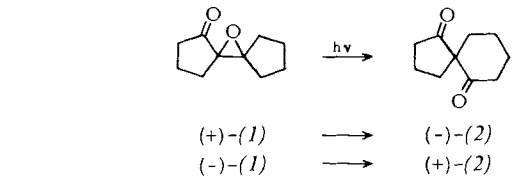
[4] *H. Gerrens, K. Kuchner*, and *G. Ley*, Chemie-Ing.-Techn., in press.

New Developments in the Field of Steroid Ketone Photochemistry

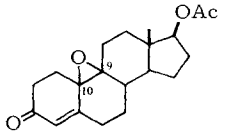
By *Kurt Schaffner*[*]

The steroids are a class of compounds which are easily modified chemically and which are suitable for studying the various structural aspects of photo-induced processes. In combination with investigations of smaller model compounds steroids often prove to be most convenient substrates for the stereochemical analysis of photoisomerizations.

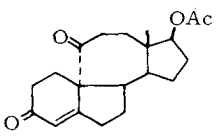
The rearrangement of α,β-epoxyketones to β-diketones has been formulated as a photolytic cleavage of the C_α-O bond and subsequent β→α-alkyl migration[1]. The reversibility of the primary photochemical step was detected by the C_α epimerization of the exocyclic oxirane of the diastereoisomeric pulegone epoxide[2]. The stereospecific isomerization of the epoxyketones (+)-*(1)* and (−)-*(1)* to the enantiomeric spiroketones *(2)* now indicates however that the second step can be rapid enough to compete with rotation about the C_α–C_β bond in the primary product[3]. Results with 3-oxo-4,5-oxido steroids had



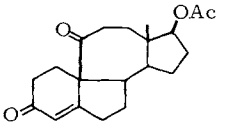
(+)-*(1)* ⟶ (−)-*(2)*
(−)-*(1)* ⟶ (+)-*(2)*



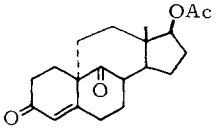
(3) 9α, 10α
(4) 9β, 10β



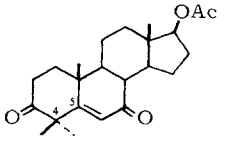
(5)



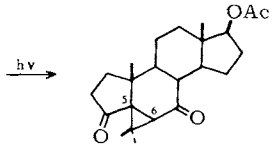
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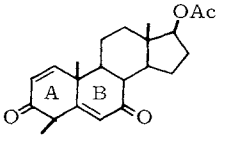
(7)



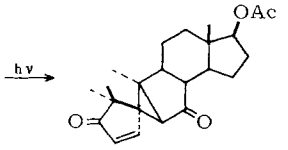
(8)



(9) 5α, 6α
(10) 5β, 6β



(11)



(12)

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[1] *O. Jeger, K. Schaffner*, and *H. Wehrli*, Pure Appl. Chem. *9*, 555 (1964).

[2] *C. K. Johnson, B. Dominy*, and *W. Reusch*, J. Amer. Chem. Soc. *85*, 3894 (1963).

[3] *H. J. Wüthrich, A. Siewinski, K. Schaffner*, and *O. Jeger*, unpublished results. Determination of the chirality of *(1)* and *(2)* and the optical yields of the photolysis *(1)*→*(2)* are in progress.

[4] *H. Wehrli, C. Lehmann, T. Iizuka, K. Schaffner*, and *O. Jeger*, Helv. Chim. Acta *50*, 2403 (1967).

[5] *M. Debono, R. M. Molloy, D. Bauer, T. Iizuka, K. Schaffner*, and *O. Jeger*, J. Amer. Chem. Soc. *92*, 420 (1970); *D. Bauer, K. Schaffner*, and *O. Jeger*, unpublished results.

[6] *S. Domb* and *K. Schaffner*, Helv. Chim. Acta *53*, 677 (1970).

[7] *S. Domb* and *K. Schaffner*, Helv. Chim. Acta *53*, 1765 (1970).

shown that the β→α-alkyl shifts are subject to a stereoelectronic control, which provides selectivity with respect to the migrating group and stereospecificity of the rearrangement[4]. The selective isomerizations *(3)→(5)* (at −65 °C) and *(4)→(6)+(7)* (at room temperature) apparently reflect the influence of such factors, which in the case of *(3)* at higher reaction temperatures may not be sufficient to prevent a transformation such as *(3)→(7)*, which presumably proceeds *via* an additional radical intermediate step[5].

Introduction of a 4α-CD_3 group can be used as a stereochemical probe for differentiating between a concerted $[_{\sigma}2+_{\pi}2]$ addition and a stepwise reaction sequence in the rearrangement of α,β-unsaturated δ-ketone *(8)* to the cyclopropyl ketones *(9)* and *(10)*. The different geminal methyl groups on C-4 in the product of type *(9)* and *(10)* resulting from labeled enedione were sterically equilibrated, while recovered starting material exhibited no such isomerization[6]. This finding rules out a concerted process and demands an intermediate product in which the steric equilibration is effected by rotation about the C-4–C-5 bond.

In the case of the bis-enone *(11)* the question arises as to which enone grouping is to be ascribed the excitation state which induces rearrangement to *(12)*. The reactions of *(8)* and *(11)* are quenched by suitable triplet energy acceptors. A combination of phosphorescence studies on *(8)* and *(11)* and ring-A and ring-B model enone compounds and the use of sensitizers and quenchers with various triplet energies showed that E_T (Ring A) < E_T (Ring B) and that the triplet energy of the reactive state of *(11)* is localized in the Ring A enone[7].

Lecture at Freiburg on December 18, 1970 [VB 267 IE]
German version: Angew. Chem. *83*, 180 (1971)

SELECTED ABSTRACTS

The photoisomerization of 1,2,4-trifluorobenzene in the vapor phase with light of wavelength 254 nm leads, according to *G. P. Semeluk* and *R. D. S. Stevens*, to two main products. After separation by gas chromatography, the products were identified by IR, NMR, and mass spectroscopy as 1,2,5-trifluorobicyclo[2.2.0]hexa-2,5-diene *(1)* and 2,3,5-trifluorobicyclo-[2.2.0]hexa-2,5-diene *(2)*. Quantum yields are low. Oxygen at 674 torr does not completely prevent formation of either compound, which can be regarded as trifluoro-Dewar-benzenes. This would suggest formation from the excited singlet state of 1,2,4-trifluorobenzene and not from the triplet state.

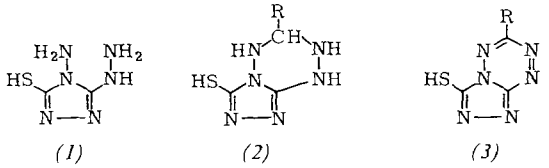


(1) *(2)*

/ Chem. Commun. *1970*, 1720 / –Ma.

[Rd 301 IE]

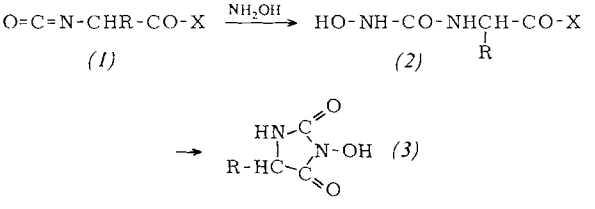
A new sensitive and specific reaction for the detection of aldehydes is reported by *R. G. Dickinson* and *N. W. Jacobson*. 4-Amino-3-hydrazino-5-mercapto-1,2,4-triazole *(1)*, which can be easily prepared from hydrazine hydrate and numerous open-chain or cyclic thioureido compounds, condenses with the formyl group in 1 N NaOH to give the unstable, oxygen-sensitive tetrahydrotriazolo[4,3-*b*]tetrazine *(2)*, which is rapidly oxidized to the violet compound *(3)* by atmospheric oxygen. The color depends on the substituent R (absorption at 520–555 nm). Reaction is still detectable at concentrations as low as 10^{-4} mole/l. Ketones, esters, amides, hydrazines, hydroxylamines, quinones, aminophenols, urea, and formic acid do not give violet condensation products. / Chem. Commun. *1970*, 1719 / –Ma.



(1) *(2)* *(3)*

[Rd 302 IE]

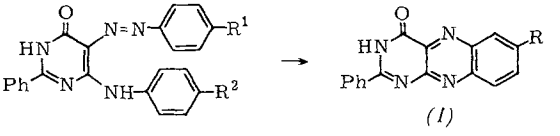
3-Hydroxyhydantoins *(3)*, **a new class of cyclic diacylated hydroxylamines,** are readily obtained by reaction of α-isocyanato fatty acids with hydroxylamine in dioxane-methanol according to a report by *P. Fankhauser* and *M. Brenner*. The reaction proceeds *via* an intermediate α-hydroxyureido fatty acid ester *(2)*. Assignment of structure follows from Exner correlations of the IR, NMR, and mass spectra. 3-Hydroxyhydantoins *(3)*, like hydantoins, are easily hydrolyzed. Examples: R = H, parent amino acid glycine, 90% yield, CH_3, DL-alanine, 85%; $C_6H_5CH_2$, DL-phenylalanine, 70%; $(CH_3)_2CHCH_2$, DL-leucine, 50%; $(CH_3)_2CH$, DL-valine, 60%. / Helv. Chim. Acta *53*, 2298 (1970) / –Ma.



(1) *(2)* *(3)*

[Rd 305 IE]

A new alloxazine synthesis is reported by *F. Yoneda, M. Ichiba, K. Ogiwara*, and *S. Nishigaki*. Heating of 6-anilino-4-hydroxy-5-*p*-nitrophenylazo-2-phenylpyrimidines with 10% sulfuric acid in glacial acetic acid (130–140 °C, 3 h) gives 2-phenyl-2-deoxyalloxazine *(1)* in 83% yield. No cyclization took place in the presence of acetic acid or trifluoroacetic acid alone. The 5-phenyl and 2-*p*-chlorophenylazo compounds could not be cyclized. Important factors affecting the reaction include the acid



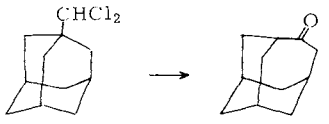
(1)

R^1 = NO_2, R^2 = H, Cl, Br R = H, Cl, Br (83,84,92%)

ity of the solvent (no reaction with 20% H_2SO_4) and the presence of a strongly electron-attracting group such as NO_2 in the 5-phenylazo substituent. / Chem. Commun. *1971*, 23 / –Ma.

[Rd 306 IE]

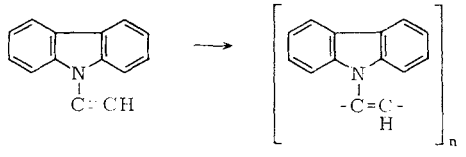
Dichloromethyladamantanes have been obtained by *I. Tabushi, Z. Yoshida,* and *N. Takahashi* by dichlorocarbene insertion into adamantane, methyladamantane, and dimethyladamantane. The hydrocarbon was allowed to react in aqueous NaOH/benzene in presence of trimethylbenzylammonium chloride with chloroform as source of dichlorocarbene (yield of 1-dichloromethyladamantane *(1)* 91% with respect to unchanged adamantane). The insertion reaction is also applicable to cyclic and acyclic hydrocarbons. When heated with 85% phosphoric acid at 110–130°C in an atmosphere of nitrogen, compound *(1)* undergoes hydrolytic rearrangement to give homoadamantanone *(2)* (69%) along with some 1-adamantanecarboxaldehyde (6%). At higher temperatures the latter is one of the main products. Formation of *(2)* probably proceeds *via* an intermediate carbonium ion. / J. Amer. Chem. Soc. *92*, 6670 (1970) / –Ma.



(1) *(2)*

[Rd 303 IE]

Synthesis and properties of *N*-ethynylcarbazole *(1)* and poly-*N*-ethynylcarbazole *(2)* are reported by *Y. Okamoto* and *S. K. Kundu*. *N*-Acetylcarbazole reacts with PCl_5 in boiling benzene or toluene to give *N*-(α,β-dichlorovinyl)carbazole, which affords *N*-ethynylcarbazole (m. p. 58°C, yield 31%) on treatment with $NaNH_2$ in liquid NH_3 followed by decomposition with NH_4Cl. Thermal polymerization of *(1)* in toluene or cyclohexane or without a solvent at 100–120°C in an evacuated sealed tube gave a dark brown polymer *(2)* having a molecular weight of 1530–1960 (*n* approximately 8–10). The conductivity of the

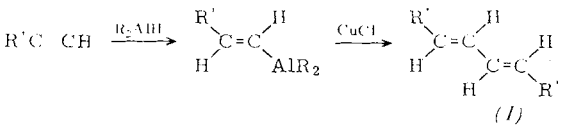


(1) *(2)*

polymer was 10^3 times as high as that of poly-*N*-vinylcarbazole; however, it possessed no photoconductivity. / J. Org. Chem. *35*, 4250 (1970) / –Ma.

[Rd 309 IE]

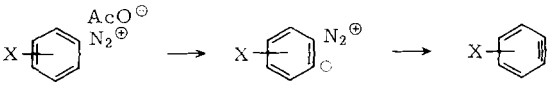
A novel stereoselective synthesis of 1,3-dienes from terminal alkynes is described by *G. Zweifel* and *R. L. Miller*. For example, when vinylalane, which is formed by the hydroalumination reaction from 1-hexyne and diisobutylaluminum hydride, is treated with CuCl in THF at 25°C copper precipitates out and coupling takes place to give isomer-free *trans,trans*-5,7-dodecadiene *(1)* (R' = C_4H_9) in 73% yield. Increasing the size of the alkyl group attached to the triple bond has little effect on the yield and stereochemistry of the diene formed. The coupling reaction with CuCl is also applicable to vinylalanes derived from disubstituted alkynes. The reaction probably proceeds *via* the vinyl-Cu(I) compounds. Examples: Alkyne: C_5H_{11}–C≡CH → 1,4-dicyclopentyl-*trans,trans*-1,3-butadiene, 68%; *tert*-butyl-C≡CH → 2,2,7,7-tetramethyl-*trans,trans*-3,5-octadiene, 67%; $C_2H_5C{\equiv}CC_2H_5$ → 4,5-diethyl-*trans,trans*-3,5-octadiene, 71%. / J. Amer. Chem. Soc. *92*, 6678 (1970) / –Ma.



(1)

[Rd 304 IE]

A simple one-step conversion of aniline into dehydrobenzene has been observed by *J. I. G. Cadogan, J. R. Mitchell,* and *J. T. Sharp*. Reaction of aniline, pentyl nitrite, and acetic anhydride with 2,3,4,5-tetraphenylcyclopentadienone in benzene at 80°C gave 1,2,3,4-tetraphenylnaphthalene in 32% yield. *m*-Bromo-, *m*-chloro-, *m*-methoxy-, and *m*-methylaniline behaved analogously. Reaction of aniline in the presence of anthracene as acceptor yielded triptycene in 10% yield. Better results were obtained with the system *p*-chlorobenzoyl nitrite/acetanilide



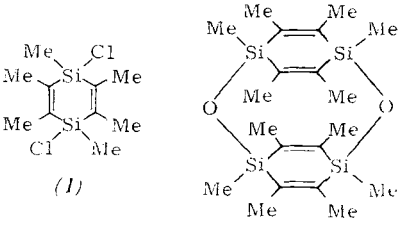
which gave the benzyne adduct in 50% yield. The reaction requires acetate ions. / Chem. Commun. *1971*, 1 / –Ma.

[Rd 307 IE]

The synthesis of 3,5-disubstituted cyclopentenes by ozonolysis of norbornadiene is described by *C. A. Grob* and *H. R. Pfaendler*. The ozonization product obtained at −70°C in methanol reacts with Ag_2O to give cyclopent-4-ene-*cis*-1,3-dicarboxylic acid, and on Lindlar reduction over a Pd-lead carbonate catalyst it gives the hitherto unknown cyclopent-4-ene-*cis*-1,3-dicarbaldehyde, which affords the saturated aldehyde on treatment with Pd/H_2. Reduction of the ozonization product with $NaBH_4$ leads to *cis*-1,3-bis(hydroxymethyl)cyclopent-4-ene. Reduction of its bis-tosylate with $LiAlH_4$ gives *cis*-3,5-dimethylcyclopentene. / Helv. Chim. Acta *53*, 2156 (1970) / –Ma.

[Rd 308 IE]

An organosilicon cyclophane *(2)* has been synthesized by *F. Wudl, R. D. Allendoerfer, J. Demirgian,* and *J. M. Robbins*. Treatment of 1,4-dichlorohexamethyl-1,4-disilacyclohexa-2,5-diene *(1)* with hydrazine gave a crystalline compound *(2)* (1–5% yield) alongside polymeric products. A further synthesis, which provided proof of structure, consists in the reaction of equimolar amounts of *(1)* and 1,4-dihydroxyhexamethyl-1,4-disilacyclohexa-2,5-diene in the presence of triethylamine in highly dilute, anhydrous solution in THF to give *(2)*, again alongside polymeric material. Compound *(2)*, which crystallizes as hexa-



(1)

gonal prisms from ether, is thermally stable and sublimes at *ca.* 268°C. NMR, mass, and IR spectra all confirm the structure. Additional proof is provided by the ESR spectrum of the green radical anion formed on reduction of *(2)* with potassium in dimethoxyethane at −80°C. / Chem. Commun. *1971*, 50 / –Ma.

[Rd 310 IE]

Methylchlorocarbene has been obtained by *R. A. Moss* and *A. Mamantov* by photolysis of methylchlorodiazirine (λ >300 nm) in tetramethylethylene, trimethylethylene, isobutene, *cis*-butene, and *trans*-butene. Addition to give the expected cyclopropanes occurred, and at 25–30°C the relative reactivities were 3.87, 2.44, 1.00, 0.74, and 0.52. The addition to *cis*-butene and to *trans*-butene was stereospecific. Vinyl chloride was formed simultaneously by rearrangement of methylchlorocarbene. / J. Amer. Chem. Soc. *92*, 6951 (1970) / –Ma.

[Rd 311 IE]

Atlas der Kunststoff-Analyse (Atlas of Plastics Analysis). Vol. I: High Polymers and Resins. Spectra and Methods of Identification. By *D. Hummel* and *F. Scholl*. Carl Hanser Verlag, Munich, and Verlag Chemie, Weinheim/Bergstr. 1968. 1st Edit. Part 1: Text. xi, 223 pp., 53 figures, 64 tables. Part 2: spectra, tables, index. 615 pp. with 1758 spectra. Plastic binding. Price for Volume I (2 parts) DM 228. The subscription price finishes on publication of Volume II. Volume I will then cost DM 260.

The Atlas of Plastics Analysis is intended as an aid to the rapid identification of polymers. To this end Part I describes methods of chemical analysis and Part II shows many IR spectra with a broad range of wavelengths. The book includes supplementary data on the thermal behavior, density, refractive index, solubility and dielectric constants of polymers and on special uses of gas chromatography, paper chromatography, thin-layer chromatography, and pyrolysis mass spectrometry. Nuclear resonance spectra are not given.

While the authors refer to more comprehensive descriptions of chemical analysis, they give only a brief account of the relevant principles. This is adequate for the specialist but is probably not informative enough for the beginner. The same is true of the separation processes. If importance is attached not only to the separation of fillers and plasticizers but also to the isolation of the anti-agers, accelerators, lubricants, antistatics, and catalysts, the separation processes prescribed for the substance classes have to be considerably altered in accordance with the problem and the polymer. Moreover, the separation methods developed for polymer analysis, *e. g.* fractionation processes, gel chromatography, and electrophoresis, are not described. The book limits itself mainly to identification of the substances and omits the physical methods that are usually important within the context of polymer analysis, *i. e.* the determination of molecular weights and their distributions, chemical nonuniformities and sequence length distributions, long-chain branching and microgel, coil, and particle sizes, crystallization characteristics, orientations, aggregations, and morphological structures, and network densities.

The book provides a broad and very useful basis for the identification of polymers.

Martin Hoffmann [NB 928 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 8th, completely revised edition. Edited by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in the Max-Planck-Gesellschaft zur Förderung der Wissenschaften under the direction of *Margot Becke-Goehring*. Verlag Chemie GmbH., Weinheim/Bergstr.[1]

System No. 61: Silver: Part A, 1.
History. Occurrence. Principal editor: *Karl-Christian Buschbeck*. 1970. iv, vii, 144 pp., linen, DM 180.–.

The introductory chapter (31 pp.) recounts the very long history of silver and its compounds. A particularly interesting feature is the description of the smelting processes, which vary with the nature of the ore and its source. Among the silver compounds, the nitrate, chloride, sulfate, and fulminate in particular have long histories. Almost a whole page is devoted to alchemical specifications for the preparation of the Arbor Philosophorum or the Arbor Dianae (experiments which work – The reviewer).

The following chapter is entitled "Cosmochemistry" and gives information on the occurrence of silver in stars and meteorites. A chapter on the geochemistry of silver is subdivided into sections on crystallochemistry, geochemical characteristics, and the frequency and occurrence of silver in the lithosphere and hydrosphere. There is also a section devoted to silver in the atmosphere, less perhaps for the sake of completeness than for the sake of curiosity: on June 14, 1956 there was a rain storm over München and the insoluble residues of the rain contained ^{111}Ag. A short section on the circulation of silver, which describes its route through the individual geospheres, concludes the chapter. A further chapter describes all silver-containing minerals, their paragenesis and their physical and chemical properties. The most important deposits and the relevant production figures are summarized in the final chapter "Production Statistics and Important Deposits".
The references in this volume go up to 1968 and in some cases even later.

System No. 61: Silver: Part A, 2.
Technology and Preparation. Isotopes. Atom. Molecules. Physical Properties of the Metal. Principal editor: *Franz Seuferling*. 1970. vi, xvi, 350 pp., 76 figures, linen, DM 421.–.
This volume is devoted entirely to elementary silver. 70 pages deal with the technology and preparation of the metal. In the main, pyrometallurgical processes are used for its extraction from silver-containing lead ores and from pure silver ores. The author describes these in detail. Hydrometallurgical processes, the most important of these being leaching with inorganic cyanides, are of minor importance in the total production of silver. The same is true of the amalgam processes. The extraction of crude silver from the anode sludge of electrolytic copper refining baths is of greater technological importance, since 18% of the world silver production is obtained from copper ores. A large number of techniques are used to process these ores, the choice depending on the nature and concentration of the admixtures.

A further section deals with the purification of crude silver. The largest part of this deals with the electrolytic separation of silver. Only the size of the section in question (about 20 pages) gives any indication of the technical importance of the recovery of silver from scrap, photographic baths, waste, *etc.* This is followed by two short sections giving exhaustive information on purity testing and the preparation of special forms of silver such as powder, sponge, wool, thread, mirrors, and films. The remainder of the book will interest the physicist more than the chemist. The chapter on the isotopes of silver deals with the preparation, separation, accumulation, and properties of Ag isotopes. The chapter entitled "Atom and Molecules" relates to work connected with electron configuration, wave functions, polarizability, atomic and ionic radii, and the optical and X-ray spectra of the atom and atomic ions.

This volume is also very up to date. The references are complete up to 1968 and some relate to works published after this date.

Ekkehard Fluck [NB 929 IE]

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[1] Cf. Angew. Chem. internat. Edit. *9*, 913 (1970).

Quantenmechanik und Theorie des Molekülbaues (Quantum Mechanics and the Theory of Molecular Structure). By *W. M. Tatewski*. Verlag Chemie GmbH, Weinheim/Bergstr. 1969. 1st Edit., 126 pp., numerous figures, stitched, DM 19.50.

The title of this book is misleading; it is not an introduction to current theory of chemical bonds and the electron structure of molecules. The author has instead set out to show, on the basis of quantum mechanics, how well founded the concepts and laws of classical structure theory are and where they can be applied. He comes to the conclusion that at present it is not possible in the case of polyatomic molecules to derive either exactly or even approximately the concept of chemical bonding or the structural formula from the general principles of quantum mechanics. The only generally valid theoretical criterion for the stability or instability of the states of a system of nuclei and electrons is the presence or otherwise of a minimum in the corresponding energy surface.

The usual concepts of theoretical chemistry, for example valence electrons, electron pair bonding, σ-π-separation, and localization or delocalization of electrons, naturally have no place in such a strict quantum theory of molecular structure. This argument

is presented in very convincing manner, but it will be of little help to the chemist in his attempts to understand the relationships between the structure and properties of molecules.

Martin Klessinger [NB 930 IE]

X. FATIPEC-Kongressbuch (10th FATIPEC Congress Report). 1970. Edited by the Scientific Committee of the 10th FATIPEC Congress. Verlag Chemie GmbH., Weinheim/Bergstr.: 1970. 1st Edit., 601 pp., numerous figures, bound, DM 98.–.

The two-yearly congress of the Fédération d'Association de Techniciens des Industries des Peintures, Vernis, Emaux et Encres d'Imprimerie de L'Europe Continentale (FATIPEC) is the largest and one of the most important scientific and technical conventions in the field of paints, lacquers, printing inks, and pigments. The 1970 FATIPEC Congress in Montreux had as its main themes the durability and decomposition of modern coatings as dependent on formulation, the preparation of the base and application, and the properties of printing inks as dependent on formulation, manufacture, the material to be printed on, and the printing process.

In addition to the ten general lectures, all the lectures (about 60) on pigments, vehicles, solvents and wetting agents, on the chemistry, physics, and structure of coatings, weathering, the effects of light and heat, corrosion and substrate, electrophoresis, mathematical statistics, optimization, and printing inks are reproduced in the book.

The lectures cover themes ranging from the theoretical to the practical end of the spectrum. It is easy to see that when the program was drawn up importance was attached to the scientific treatment of basic and practical themes alike.

The FATIPEC Congress report, as always, gives a comprehensive survey of the current problems and progress in this field of technology. Its completeness is almost unrivaled.

Werner Funke [NB 931 IE]

The Synthesis and Characterization of Inorganic Compounds. By *W. L. Jolly.* Prentice Hall International, Hearts 1970. 1st Edit., xi, 590 pp., bound, *ca.* DM 74.–.

The first three chapters of this book deal with the fundamentals of synthesis, preparative methods, and characterization of compounds, while the fourth gives procedures for the preparation of inorganic compounds.

The first chapter describes the thermodynamic and kinetic aspects of the synthesis of compounds. The second chapter deals with the methods commonly used in the laboratory: purification and drying of solvents, operations in inert atmospheres, in vacuum, and under pressure, measurements of low and high pressures, purification of compounds, high- and low-temperature techniques, *etc.*

The third chapter is devoted to the characterization of substances and to determination of their structures, greatest emphasis being placed on instrumental methods, such as IR, UV, NMR, ESR and mass spectroscopy. Procedures for the preparation of a large number of interesting inorganic compounds are given in the fourth chapter. The substances are so chosen that materials from the earlier sections can be used in later ones. The preparations are well chosen as representative of the whole range of inorganic chemistry and the most important working methods involved. Glass blowing, safety precautions, and first aid are reviewed in an appendix, and tables are given of things such as irreducible representations of important symmetry groups. Each chapter provides access to further information by means of literature references, and also a series of exercises.

This book thus contains all the information that a good preparative inorganic chemist must have at his command, and at the same time shows the high demands which are made on his versatility. The general appearance and printing are very attractive; the work is clearly divided up into sections, and easy to understand. It is particularly recommended to all those who have to organize inorganic practical work for advanced students, and to the students themselves. Even preparative chemists who are not working in the field of inorganic chemistry will find a wealth of valable information in this book.

Alois Haas [NB 941 IE]

Phase Diagrams, Materials, Science and Technology. Vol. I: Theory, Principles and Techniques of Phase Diagrams. By *A. M. Alper.* Academic Press, New York – London 1970. 1st Edit., xviii, 358 pp., numerous figures, bound $ 16.00.

This book, which is the first of three volumes, correlates in its opening sections the thermodynamic theory of phase diagrams with the results of recent computer investigations. In the main these chapters aim at drawing conclusions from thermodynamic data such as heats of fusion and heats of mixing on the structure of melting diagrams and phase diagrams or *vice versa, i.e.* at drawing conclusions on thermodynamic data of the type mentioned from diagrams obtained experimentally. The thermodynamic relationships necessary for this are set out very clearly, with the relevant diagrams in a section written by *Y. K. Rao.* The results of computer calculations on this thermodynamic basis are given in a contribution by *L. Kaufmann* and *H. Bernstein,* who deal in great detail with a large number of metal alloy systems.

Three larger sections follow on the experimental determination of phase diagrams *(J. Macchesney* and *P. Rosenberg),* the interpretation of experimentally obtained diagrams *(H. C. Yeh)* and their use in obtaining or preparing solid phases of a desired constitution *(W. A. Tiller).* These sections deal in detail with all modern experimental methods such as dilatometric and electrochemical investigations (EMF methods), conductivity measurements, thermogravimetric methods, X-ray analysis and the classical methods.

Two shorter sections on the very modern field of high pressure investigations *(A. Jayaraman* and *L. H. Cohen)* and on metastable systems and their application in the preparation of refractory systems *(T. P. Seward)* complete this first volume.

This book fulfils a valuable function with respect to solid state technology, particularly the technology of metal alloys, a subject which in recent years has become very important for many fields of endeavor (space technology, reactor technology, *etc.*) and can therefore be recommended to all who intend to work and carry out research in the newest fields of this branch of science.

Klaus Schafter [NB 933 IE]

Biologische Zerstörung der makromolekularen Werkstoffe (Biological Destruction of Macromolecular Materials). In the series Chemie, Physik und Technologie der Kunststoffe in Einzeldarstellungen, Vol. 15. By *H. H. M. Haldenwanger.* Springer Verlag, Berlin – Heidelberg – New York, 1970. 1st Edit., viii, 283 pages, bound, DM 58.–.

This "piece of writing", which is how *Haldenwanger* described his book, is the astonishing work of a blind author. After *Haldenwanger's* death the manuscript was skilfully revised and condensed by *G. H. Göttner.*

The book is arranged on the basis of the most important groups of pests. In the 16 chapters that this system of classification gives rise to, the most important organic materials and their resistance to biological attack are discussed. The detailed reproduction of test specifications saves the biologist the trouble of sorting through the original literature. The comparison of the various test results and the critical comments on these are extremely valuable.

A chemist might also have liked to see the book arranged along technological lines. The polyethylene specialist, for example, has to sort out the test results that interest him from each individual chapter. The short subject index is not very helpful either, since only general entries are included on polyolefins or polyvinyl compounds.

The comprehensive 43-page appendix of tables, twelve of which summarize formulas, the most important fungicides, biocides, insecticides, harmful organisms, and softeners for plastics, makes the book immensely clear and informative. Exhaustive

references are quoted for work published up to 1967. This excellent book would have been even more valuable if the chemical compounds mentioned had been cited not only by name, which is by no means a clear system and which in the present case has led to a few errors, but also in the form of structural formulas.

With the above reservations, however, the book as a whole can be recommended as a work of reference for biologists, chemists, and practical technologists alike.

H. Alberts [NB 934 IE]

Organosilicon Heteropolymers and Heterocompounds. By *S. N. Borisov, M. G. Voronkov,* and *E. Ya. Lukevits.* From the series Monographs in Inorganic Chemistry. Plenum Press, New York, 1970. 1st Edit., xx, 632 pp., bound, $ 40.00.

The present work is an English translation of a Russian monograph which was published in 1966. Of the authors, *M. G. Voronkov* ranks as one of the most active research workers in the field of organosilicon compounds, while *Borisov*'s premature death in an accident was a sad loss to science.

Stimulated by the success of organosiloxane chemistry, researchers have recently turned more and more toward the chemistry of organic silicon compounds containing hetero atoms, and Soviet research workers have been involved strongly in this trend. A summary of the current state of knowledge by Russian authors is thus to be welcomed, particularly in view of the difficulties posed by the Russian literature. Admittedly the term "current" is a relative one – the literature is covered up to May 1, 1965 – but this, as we know only too well, is a common failing with translations.

The book deals with low- and high-molecular compounds containing the groups ≡Si-M, ≡Si-O-M, ≡Si-N-M, and ≡Si-C-M. The method of preparation, physical properties, chemical behavior, and possible applications are described in each case. The known data on definite low-molecular compounds of the classes considered are summarized in numerous tables.

This is the first complete compilation of the material in this form. The amount of knowledge that has been accumulated in such a relatively short time will astound even the initiated. This is a reference book which will provide much needed help for the worker in the field of organometallic chemistry.

The fact that in the future many details in the material reviewed may require revision is surely only a reflection on the newness of the subject. In particular, as far as the practical aspects are concerned – *de facto* the technical significance of the organic heterocompounds of silicon is small outside the USSR – it will be necessary to go through many of the literature recommendations with a critical eye and sort the wheat from the chaff.

To a western reader it may seem odd, to say the least, to find the literature references (of which there are almost 1750) separated into those by Soviet and those by non-Soviet authors, and also to find all the authors' patents listed. As *Goethe* says, "There is no such thing as nationalistic art or nationalistic science. Both belong, like all else that is great and good, to the entire world".

Walter Noll [NB 935 IE]

Manual on Radiation Dosimetry. Edited by *N. W. Holm* and *R. J. Berry.* Marcel Dekker, Inc., New York, 1970. 1st Edit., xvi, 450 pp., numerous figures, bound, $ 24.50.

The editors' intention has been to create once and for all a handbook which in its shape and weight is genuinely a "hand-book", a book, in fact, which can easily be carried around. This book is intended for scientists, engineers, and technicians who are daily confronted with practical problems of dosimetry. The book is divided into two parts. The first part contains chapters on methods of dosimetry and on the various fields of application, such as radiation protection, radiation therapy, ^{60}Co and accelerator dosimetry. The second part gives 20 sets of precise instructions for the operation of the various dose measurement processes which can be used in experimental work. As in a larger "handbook", the individual chapters are written by experts of international renown in their fields, which of course results in a certain degree of unevenness both in the presentation and in the selection of references. The index helps one to track down all the mentions of a given topic which is covered in different chapters. The book is a veritable mine of information for anyone concerned with chemical dosimetry techniques in the widest sense, and the extensive tables contribute toward this, but anyone working on neutron or accident dosimetry in reactors will search in vain for his keywords. The book is undoubtedly a valuable addition to any library.

H. Kiefer [NB 943 IE]

Organic Peroxides. Vol. 1. Edited by *D. Swern.* John Wiley and Sons Ltd. New York – London 1970. 1st Edit., x, 654 pp., numerous figures, bound, £ 15.00.

The chemistry of the organic peroxides was discussed in 1961 in two extremely good but relatively short books by *Davies* and *Hawkins.* The present book is the first section of a three-volume work, written by a group of authors with personal experience in the field of peroxide chemistry.

While the introductory chapter (104 pp.) does not give much more information than the books mentioned above, the second chapter by *Benson* and *Shaw* on the thermochemistry of organic peroxides (35 pp., with numerous tables) contains novel and useful information. The next three chapters (125 pp. in all) deal with the rearrangements of peroxy radicals, the reactions of peroxides with nucleophiles, and the synthesis and decomposition of peroxy esters. The two chapters by *Swern* (195 pp.) on the preparation and the physical properties of peroxy acids are remarkable in their attention to minute experimental details. Three chapters by *Sosnovsky* (90 pp.) describe the base-catalyzed autoxidation and the metal ion-catalyzed decomposition of symmetrical peroxides and peroxy esters. A final short chapter is devoted to polymerization with the aid of peroxides and its kinetics.

In a work by a number of authors it is impossible to avoid a certain fluctuation in quality. Notwithstanding this, it is extremely valuable to have information on peroxides collected together into one place, in a form as up-to-date and as complete as possible. Indeed, it is almost too complete, because in the tables on pp. 31 and 241 we find the as yet undiscovered ozonide of tetramethylethylene, and the ozonide of fluorenone which was deleted from the literature some twenty years ago! However, too much emphasis should not be placed on these minor shortcomings. A critical evaluation will only be possible after the publication of the two remaining volumes, which it is to be hoped will take place as soon as possible.

Rudolf Criegee [NB 944 IE]

The Alkaloids. Edited by *R. H. F. Manske.* Academic Press, New York – London. Vol. XI: 1st Edit. 1968, xvi, 549 pp., numerous equations, bound $ 26.00. Vol. XII: 1st Edit. 1970, xvii, 637 pp., numerous equations, bound, $ 29.00.

In the 20 years since the appearance of the first volume, *Manske*'s "The Alkaloids"[1] has become a household word for all chemists concerned with natural products, even if its character has in part changed; from vol. XI onward "The Alkaloids" became principally a summary of progress in the chemistry of alkaloids from individual plant species. For the most part the articles refer back to others previously published in this collection.

Nine of the twelve chapters of vol. XI are devoted to indole compounds. In this balanced survey practically the whole range is considered; of the major groups, only the ergot alkaloids are not included. Further sections deal with the alkaloids of the Amaryllidaceae and colchicine with related compounds, and the last chapter is concerned with pyridine alkaloids, which throughout is an amplification of the corresponding chapters which appeared more than ten years ago in vol. VI.

The most interesting features of vol. XII are the two extensive chapters on diterpene alkaloids, since this is the area in which there has been considerable progress in the last few years. The present survey is in fact the first one in which it has been possible

to evaluate a large number of known structures. One minor failing is the unclear way in which the formulas are numbered, which could give rise to errors. The chapter devoted to the indole alkaloids of Alstonia species is a supplement to the first nine chapters of vol. XI. The chapters on the alkaloids of the Papaveraceae and of Senecio are very thorough and therefore very useful; they reflect the endeavor to use alkaloid chemistry for chemo-taxonomic purposes. The last chapter is devoted to the legal chemical aspects of alkaloid chemistry. Its social importance alone makes this chapter an essential part of the book.

The penultimate chapter, "Alkaloids Unclassified and of Unknown Structure", presents something of a problem. As a collection of all those compounds which could not be classified under any other heading due to lack of chemical information, it could have had some value. In its present form, however, it includes compounds whose classification presents no difficulties. In some cases, the same compound even appears in two places, once in this chapter and once in the appropriate chapter in the same volume (venoterpin, pp. 208 and 458; cassipourine, pp. 323 and 464). Part of the trouble is certainly due to the relatively long delay in publication; to judge from the references most of the reviews were written in 1967, since only in exceptional cases are articles published in 1968 considered.

In general, it must be said that the volumes under review, like all the previous volumes, represent an increase in our store of knowledge, and one which no library specializing in this subject can afford to be without.

Karel Bláha [NB 945 IE]

[1] Cf. Angew. Chem. internat. Edit. *6*, 192 (1967).

Tables for Use in High-Resolution Mass Spectroscopy. By *R. Bings, J.S. Littler,* and *R. L. Cleaver.* Heyden and Son Ltd., London 1970. 1st Edit., xx, 160 pp., numerous tables, DM 97.–.

The tables compiled by *Bings, Litter,* and *Cleaver* are intended to assist in the "peak matching" technique for mass determination with high-resolution mass spectrometers. The authors appear to have had AEI instruments chiefly in mind.

The first table gives the most important mass lines in the spectra of perfluorokerosene, perfluoromethyldecalin, perfluorodimethylcyclohexane, and heptacosafluorotributylamine, which are frequently used as reference components. The table also contains factors which enable the ion masses of the mass lines of a reference substance to be converted into the ^{13}C analogs. This is extremely helpful for people whose instruments do not have a digital mass indicator; users of more modern equipment will hardly ever use these factors.

Much the same situation is found with Table 2, which contains factors for the determination of further mass lines in the reference compound. Since factors of up to 1.5 are given, while for example Varian instruments (SM 1) only permit a mass difference of about 10%, this table again can only be used fully by the possessors of certain types of instruments.

The next table contains the corresponding values for fluothane. The final table simplifies the mass determination of compounds with hetero atoms, which are composed of different isotopes. It shows in graphic form the isotope ratios for chlorine, silicon, sulfur, boron, and bromine, for increasing numbers of hetero atoms, and also combinations of chlorine and bromine atoms. It can also be used to obtain the contribution of these hetero atoms to the precise ion mass. This table is thus very useful for the mass determination of compounds containing hetero atoms, particularly as such values are not given in other collections of tables for the determination of empirical formulas.

The book is completed by an appendix containing the tried and trusted "Henneberg Tables" for mass determination.

This collection of tables is thus an important aid, but principally for those laboratories carrying out precise mass determinations with instruments not fitted with digital mass indicators. Of this limited clientele, some will undoubtedly be frightened off by the high price. This appears to be due to the attractive binding (artificial leather) rather than the contents.

Gerhard Spiteller [NB 939 IE]

Coordination Compounds. From the series Studies in Modern Chemistry. By *S. F. A. Kettle.* Thomas Nelson and Sons Ltd., London 1969. 1st Edit., vii, 220 pp., £ 1.75.

The present series now includes a monograph on coordination compounds, written by a very notable English author belonging to the younger generation of theoretical chemists. The contents are divided into eleven chapters: 1. Introduction; 2. Nomenclature and geometrical structure of coordination compounds; 3. Preparation of coordination compounds; 4. Stability of coordination compounds; 5. Crystal-field theory of transition metal complexes; 6. Ligand-field theory of transition metal complexes; 7. Electronic spectra of transition metal complexes; 8. Magnetic properties of transition metal complexes; 9. Other methods of studying coordination compounds (vibration spectroscopy, resonance spectroscopy), 10. Thermodynamic aspects; 11. Reaction kinetics of coordination compounds. There is an appendix containing brief discussions of some applications of group theory, the Russell-Saunders coupling scheme, the significance of ligand group orbitals, and examples of Tanabe-Sugano diagrams. The text is supplemented by numerous clearly arranged tables and figures.

This very clearly written monograph attempts to bridge the gap between the standard textbooks and the almost unmanageably large number of publications in the field of coordination chemistry. The author is writing mainly for advanced students, and assumes an elementary knowledge of AO and MO theory, chemical kinetics, and thermodynamics. He is principally concerned with the coordination compounds of the transition metals, but in a number of places he also draws attention to complexes of the main group elements. It is pleasant to find numerous references to the analogy between the coordination relationships in solution and in the solid state, but regrettably, there is no discussion of the large number of coordination compounds in which the central atom is formally in a lower state of oxidation. Again, a monograph like this, which deliberately goes beyond the range of the elementary textbooks, ought to have references to the more important works in the literature (*e.g.* to review articles on important sub-topics). Despite these objections, however, the book can be thoroughly recommended to any chemist whose main interest is "classical metal complexes".

Helmut Werner [NB 940 IE]

Free-Radical Chain Reactions. By *E. S. Huyser.* John Wiley and Sons Ltd., New York – London 1970. 1st Edit., 387 pp., numerous figures, bound, £ 9.50.

The study of radical chain reactions has long ranked as a domain of physical chemistry; in lectures on organic chemistry this type of reaction is usually only mentioned in passing, with reference to a few reactions, such as the chlorination of methane. Today this topic is of importance in both preparative and full-scale industrial organic chemistry, and in the present work *E. S. Huyser* has undertaken to present the basic principles of the kinetics and mechanisms of these reactions clearly and in a manner understandable by any chemist. The complicated kinetic equations are derived in so detailed a manner that even those less experienced in mathematics should be able to follow them in every detail.

Chapters 1–4 deal with the fundamentals of the mechanisms, kinetics and the relationships between structure and reactivity. The following sections are concerned with the principal types of chain reactions: aliphatic substitutions (greatest emphasis being placed on halogenation), radical additions (the compound being added and the unsaturated substrate are separately and systematically dealt with), eliminations, and radical rearrangements. A separate chapter is devoted to the chemistry of in-

itiators, but chain-termination reactions, which today have been just as thoroughly investigated, are in the reviewer's opinion dealt with too briefly. The stimulating section on redox reactions is a little uneven and could profitably have been restricted to electron-transfer reactions. The section on autoxidation could easily have fitted into the section on aliphatic substitution, for example. The last chapter gives a general survey on polymerization which makes up in breadth of coverage what it lacks in depth. No account is taken of aromatic substitutions, some of which also involve radical chains.

The discussion is always a balanced account of the current state of the art, and is clarified by a generous allocation of equations. There are places where excessive use is made of the concept of radical stability in the interpretation of reactivity relationships and bond energies. It is pleasant to report that only a few errors (*e.g.* Equation 3–142 or in the derivation on p. 53) were found.

This is an outstanding work. Every library should have a copy, and it is heartily recommended to all those interested in radical chemistry.

Christoph Rüchardt [NB 938 IE]

Rodd's Chemistry of Carbon Compounds. Edited by *S. Coffey.* Vol. II, Part D: Steroids. Elsevier Publishing Company, Amsterdam – London – New York 1970. 2nd Edit., 550 pp., 42 figures, bound, Dfl. 95[1].

In three chapters this book, the first of two volumes on steroids, deals with sterols and bile acids, steroid hormones, and cardioactive steroids.

The introductory section discusses the nomenclature and stereochemistry of this class of substances and gives details of the usual physical methods of investigation. The references to comprehensive works are very useful.

The chapter on sterols and bile acids accounts for almost 50% of the book and is a mine of information for the chemist with historical interests.

The isolation, synthesis, and modification of estrogens, androgens, and progestative and adrenocortical hormones are discussed in the second section. No mention is made, however, of the recent developments in the stereoselective total synthesis of 19-norsteroids.

The comparisons of biological intensities of action are of absolute value only if the experimental conditions (*e.g.* animal species, application, dosage range, *etc.*) do not differ. The selection of the modified sex hormones discussed seems to be very random.

Detailed information is given on the structural determination of cardioactive cardenolides and bufadienolides, but the synthesis of these substances receives only incomplete treatment.

An appendix gives the latest IUPAC rules for steroid nomenclature.

The text, with its references and physical data, makes difficult reading. The work will be particularly useful to chemists and biochemists working in the field of Sterols and Steroids. It is not very suitable for teaching purposes.

Rudolf Wiechert [NB 936 IE]

Chemische Elementarprozesse (Elementary Chemical Processes). Edited by *H. Hartmann* in collaboration with *J. Heidberg, H. Heydtmann,* and *G. H. Kohlmaier.* Springer Verlag, Berlin – Heidelberg – New York, 1968. 1st Edit., xii, 487 pp., 86 figures, bound, DM 58.–.

The present book contains a collection of lectures delivered during the 1965 Constance theoretical chemistry summer school on the subject of elementary chemical processes. In accordance with the object of the course, this book sets out to introduce advanced students and scientists in other disciplines to the latest developments in the field of reaction kinetics. It deals both with the theoretical foundations of kinetics and with modern methods for investigating elementary processes in the gas and liquid phase. Subjects like reaction cross sections and rate constants, transition state theory, potential surfaces, nonadiabatic reactions, quantum statistics of chemical reactions, unimolecular reactions, intermolecular energy transfer, and Monte Carlo calculations are discussed; molecular beams, shock waves, flow systems, and flash photolysis are also explained. The authors also deal with structure and reactivity, heats of reaction, solution reactions at high pressure, nuclear magnetic resonance, and relaxation processes for rapid reactions in solution.

Since some of the articles go far beyond the bounds of introductory material they offer new points of view even for the reader who is more familiar with this field. In fact, the term introduction cannot be applied at all to some of the contributions. As a whole, the book gives an excellent survey of the very varied fields of modern reaction kinetics, and will be used widely both as an introduction and as an aid to further study.

Jürgen Troe [NB 937 IE]

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Biogenic Substances in Sediments and Fossils[**]

By Pierre Albrecht and Guy Ourisson[*]

Most sedimentary rocks contain small concentrations of finely divided organic material. With the aid of modern analytical methods, samples of such rocks can be examined in detail, and conclusions can be drawn concerning the origin of the organic substances. Intact or modified biogenic compounds such as paraffins, isoprenoids, alcohols, ketones, carboxylic acids, steroids, triterpenes, and porphyrins have been isolated from the soluble fractions of the organic material of many sediments and from identified fossils of various geological ages. Even Precambrian rocks contain biogenic substances, so that life forms must have existed more than three billion years ago. The main component of the organic material is "kerogen", the complicated polymeric structure of which has not yet been established.

1. Introduction

It is the inorganic chemist rather than the organic chemist who is concerned with the analysis and chemistry of minerals and sediments. Organic substances, such as amber, ozocerite, and fichtelite, and naturally also petroleum and coal, are only rarely encountered in classical geochemistry.

The past ten years have seen an unexpected upsurge in the investigation of organic substances in a wide range of sedimentary rocks, fossils, and meteorites, arising from the original studies by *Treibs*[1]. This has only become possible through modern analytical methods, which allow determinations in the microgram to nanogram range.

These investigations have also led to close, friendly cooperation between geologists and organic chemists, two groups of scientists whose jargon, methods, and thought processes differ considerably.

"Organic geochemistry" is not confined to the practically important problems of the formation of petroleum, of oil shale, or of coal, but has a very comprehensive brief, which includes isolation and characterization of organic components in rocks, explanation of their origin and of the changes brought about by time and temperature as well as in reactions catalyzed by minerals (*i.e.* interpretation of their "diagenesis"), simulation of the diagenesis in the laboratory, comparison of the constituents of present-day plants and related fossils (paying due attention to their diagenesis), searches for signs of the earliest life forms or of extraterrestrial life, *etc.* Geologists, paleontologists, and chemists are particularly interested in the substances that occur intact in sediments and fossils, though also in those that are present in degraded or otherwise modified forms.

In this progress report we shall refer only briefly to the studies on meteorites and moon specimens, since these are still far from complete. We shall be concerned mainly with the organic geochemistry of the earth, and the methods and problems of this new discipline will be illustrated by relevant examples.

2. General

Most of the organic material on this earth is finely distributed in the sedimentary layers of its crust.

The total quantity of carbon on the earth is estimated to be approximately 6.4×10^{15} t, of which 5×10^{15} t is in the

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[**] General literature: *I. A. Breger*: Organic Geochemistry. Pergamon Press, London 1963; *E. T. Degens*, Geochemistry of Sediments. Prentice Hall, London 1965; *B. Nagy* and *U. Colombo*, Fundamental Aspects of Petroleum Geochemistry, Elsevier, Amsterdam 1967; *P. H. Abelson*: Researches in Geochemistry. Wiley, New York 1967, Vol. 2; *M. Calvin*: Chemical Evolution. Oxford University Press, London 1969; *G. Eglinton* and *M. T. J. Murphy*: Organic Geochemistry. Springer, Berlin 1969; see also Advan. Org. Geochem. *1962*, *1964*, *1966* and *1968*.

sediments (particularly in the shales and carbonates) and about 1.4×10^{15} t in the metamorphic rocks. By comparison, the quantity of carbon in living organisms, *i.e.* 0.003×10^{15} t, is practically negligible[2]. Even coal and petroleum, estimated to account for 1/500 and 1/16000, respectively, of the total organic material in the sediments[3], seem insignificant by comparison. These results are based on thousands of analyses by many research groups.

According to *Welte*[2], the carbon cycle may be divided into two subcycles, *i.e.* the "biochemical" cycle, whose period can be measured in days, and the "geochemical" cycle, which takes millions of years (Fig. 1). This second cycle results from the fact that about 0.01% of the total organic products in the sediments "survives". Small as this proportion seems to be, a considerable quantity of organic material accumulates and is preserved in the sediments in the course of millions of years, and there it undergoes the second cycle.

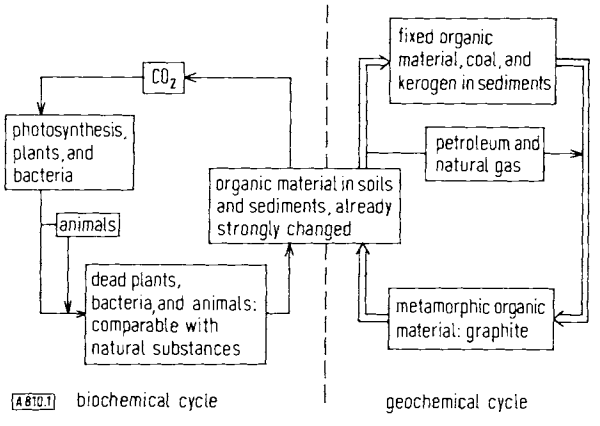


Fig. 1. Carbon cycle (after [2]). Oxygen is present in the biochemical cycle, but not in the geochemical.

The organic material occurs in the sedimentary rocks in two characteristic forms, one of which (average 10%) can be extracted with common organic solvents, while the other, known as kerogen (average 90%), is insoluble in such solvents.

Kerogen is a highly condensed polymer whose structure is still almost unknown. It can be obtained in a more or less unchanged form by dissolving the inorganic material of the rock in hydrochloric acid and hydrofluoric acid and washing it out. The kerogen forms a brown to black powder, depending on its source.

3. Methods and Analytical Procedures

An average 100-g sediment sample yields about 100–200 mg of extract, which usually has a very complex composition. Identification of the constituents may be complicated by contamination of the sample with traces of foreign substances during treatment, which necessarily involves several steps. Traces of amino acids and hydrocarbons have been detected in fingerprints[4]; plasticizers and silicones are also common contaminants in modern analytical chemistry[5]. *Hoering*[6] pointed out that many samples are wrapped in paper or in textile or plastic material for dispatch, and may therefore be contaminated even before they are received. Thus *Brandt*[7] has isolated traces of polychloro-biphenyls from a fossil fern. However, manufactured products of this nature are no longer found if the most rigorous precautions are always taken in geochemical work.

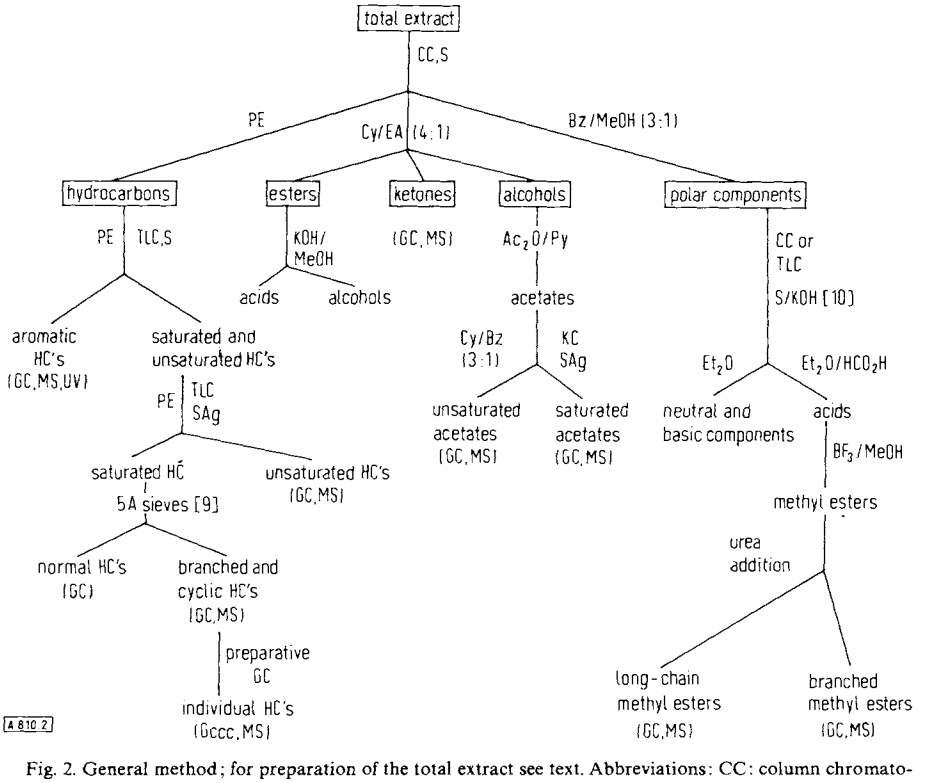


Fig. 2. General method; for preparation of the total extract see text. Abbreviations: CC: column chromatography; TLC: thin layer chromatography; S: silica gel; SAg: 10% of silver nitrate on silica gel; S/KOH: silica gel impregnated with KOH; GC: gas chromatography; GCCC: gas chromatography on capillary columns; MS: mass spectrometry; PE: petroleum ether; Cy: cyclohexane; Bz: benzene; EA: ethyl acetate; Py: pyridine; HC: hydrocarbons.

3.1. General Methods

The surface of the rock sample is first carefully scraped. The rock is then crushed into pieces measuring 2–3 cm, and is washed with 40% hydrofluoric acid, with water, and finally with benzene/methanol (3:1). The dried pieces are ground to a fine powder in a disk mill and then extracted in centrifuge tubes using ultrasound according to *McIver*[8], usually with benzene/methanol (3:1). This method is much faster and much more effective than continuous Soxhlet extraction.

After centrifugation, decantation, and evaporation of the solvent, the residue is separated chromatographically. The importance of chromatography on selected adsorbents and the significance of the 5-Å molecular sieves for the separation of linear and branched hydrocarbons can be seen in Figure 2.

The substances or mixtures isolated are characterized by the usual methods, *i.e.* UV (particularly for the aromatic compounds), IR (microcells, in some cases beam condenser), NMR (microcells, CAT), and usually mass spectrometry (preferably coupled with gas chromatography). The quantities of substance are generally only sufficient for such physical characterization, though useful guides to functional groups can be obtained *e.g.* by thin layer chromatography.

Hypothetical structures can often be deduced from such data, and can then be checked by comparison with reference substances. If no reference substance is available, X-ray structural investigations may be used. *Whitehead et al.*[11] determined the structures of some polycyclic saturated hydrocarbons from optically active petroleum fractions in this way.

4. Biogenic Substances in Sediments and Fossils (Survey)

The presence of biogenic substances in petroleum and in oil shales was first detected by *Treibs*[1] in his studies on porphyrins. Since then, nearly all classes of organic substances have been isolated at least once from sediment extracts (see Table 1). It must be expected, however, that certain biologically important macromolecules such as nucleic acids, proteins, polysaccharides, and enzymes will be extensively changed in the sediments.

Table 1. Presence of various classes of compounds in sediments and fossils.

Proteins	in fossil bones, shells [12]
Chitin	in a fossil insect [13]
Carbohydrates	present as traces in pre-Cambrian sediments [14]
Porphyrins, Amino acids, Saturated fatty acids, Alkanes	widely distributed components, also present as traces in the oldest pre-Cambrian deposits of the earth [15–18]
Triterpenes	in lignite [19]; in oil shale [20]; degradation products also in petroleum [21]
Sterols	in recent sediments [22], in oil shale [23], in lignite [24]
Carotenoids	only in recent sediments [25]; in reduced form also present in Green-River oil shale [26]

Proteins have been isolated from places that were well protected against diagenetic effects and from cavities of fossil shells and bones[12]. Chitin, a polymer of *N*-acetylglucosamine units with ether linkages, which is found in the exoskeleton of arthropods, has been isolated from a Cambrian fossil insect[13] (see Table 2).

Table 2. Geological time scale. Age of earth: 4.6×10^9 a.

Era	Formation	Divisions	Age in millions of years
Cenozoic	Quaternary	Holocene Pleistocene	2
	Tertiary	Pliocene Miocene Oligocene Eocene Paleocene	70
Mesozoic	Cretaceous	Upper Lower	135
	Jurassic	Upper Middle Lower	180
	Triassic	Upper Middle Lower	225
Paleozoic	Permian	Upper Lower	270
	Carboniferous	Upper Lower	350
	Devonian	Upper Middle Lower	400
	Silurian	–	440
	Ordovician	Upper Lower	500
	Cambrian	Upper Middle Lower	570
	Pre-Cambrian	–	

The saturated linear fatty acids and the porphyrins derived from organic pigments such as chlorophyll and hemin are best suited by their stability to withstand geological conditions without suffering excessive degradation. The alkanes also play a very important part, since these are the most stable organic compounds. They may be present in the sediment in their original form or as the final products formed from molecules that had formerly contained functional groups; alternatively, they may even be fragments of kerogen.

Substances occurring in sediments and fossils and having structures specific enough to allow the verification of their biological origin are aptly described by *Eglinton et al.*[27] as "biological markers". These may be intact or only slightly degraded biological compounds for which abiogenic synthesis appears extremely improbable.

These biological markers may provide valuable clues to the origin of the geological organic material, and may also very often be of great value as paleo-ecological markers. In the case of partly degraded products, correlation with biological precursors may allow one to build up a picture of the reactions in the sediment.

5. Former and Present-Day Biological Processes; Possibility of Paleochemotaxonomy

The organisms normally lose their original form by breakdown in the sediment, so that it is usually impossible to assign the organic material in the sediment to a certain life form. This material is very often derived from a large number of different plants and animals. In special cases, however, the organic matter of dead fauna and flora may be replaced by fine-grained rock or by minerals in such a way that the original morphology is preserved. In broad outline, this is the process by which fossils are formed.

It is conceivable that small traces of the most stable part of the original organic molecule from the plant or animal still remain in such cases.

On comparison of the organic material from very old sedimentary rocks with that from some more recent rocks, it is found (see Section 7) that the biochemical processes since the Precambrian are substantially similar to present-day processes.

To allow a direct correlation between former and present-day biochemical processes, however, it would be necessary to compare the organic substances from fossils and existing life forms of the same species or at least of a very closely related species. These comparisons are complicated by the fact that many fossil plant and animal species have now become extinct.

In a study of pigments of fossil crinoids (sea lilies) from the Jurassic period (170 million years old), *Blumer*[28] was able to isolate hydroxyquinones similar to those of present-day life forms that are related to the crinoids (see Section 6.2.2).

The Lower Triassic layers of the variegated sandstone (200 million years old) of the Vosges contain clay layers that are very rich in fossil plants. Samples containing only fossil "horse-tails" *(Equisetum brongnarti)* have been examined in some detail[29]. Since the genus *Equisetum* is still common among present-day flora, the constituents of the fossil can be compared directly with those of the fresh plant *(Equisetum silvaticum)*. The distribution of the alkanes is almost identical in both cases (Fig. 3). This similarity was also confirmed in studies by *Stransky et al.*[30] on another present-day species *Equisetum palustre*.

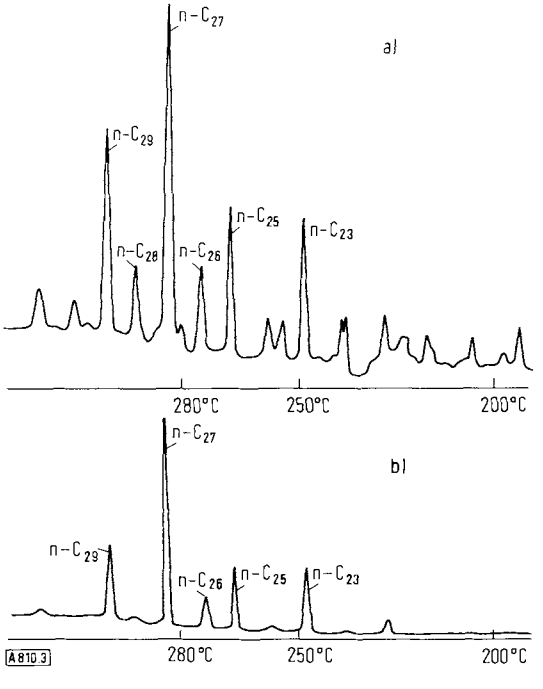


Fig. 3. Gas chromatograms of the saturated hydrocarbons from (a) fossil and (b) modern *Equisetum* (after [29]).

The *n*-alkanes are important constituents of the cuticle, and are synthesized in the present-day plants in definite proportions, though these vary from family to family. A chemotaxonomic classification is therefore possible in some cases[31]. The investigations mentioned above thus show that at least a small part of the original cuticle alkanes may persist in the fossil plants if these are not buried too deeply, *i.e.* at low temperatures and pressures; they therefore open the way to paleochemotaxonomy. This possibility is particularly interesting because intact plants are frequently not available for conventional taxonomy, and analyses of the type described can be carried out on incomplete specimens.

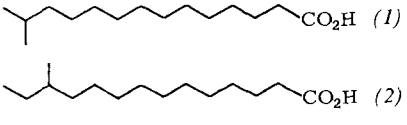
6. The Fate of Biological Substances under Geological Conditions

The organic material is exposed to numerous diagenetic attacks in the sediment. These attacks are evident in various stages of diagenesis, and can be divided into three main groups. Enzymatic and microbiological processes undoubtedly occur in the early stages of sedimentation. Physicochemical effects (acidic-basic and oxidizing-reducing conditions) operate in these and in subsequent stages ("early diagenesis"). Finally, during the sinking of a sediment, important changes are effected in the organic material by rising temperature, increased pressure, and catalytic effects of the rock.

6.1. Enzymatic, Microbiological, and Other Changes in the First Stages of Sedimentation

Enzymatic changes, particularly to complex biogenic polymers (proteins, polynucleotides, *etc.*), can take place shortly after the death of the organisms. Other "spontaneous" changes result from autoxidation. Amber, for example, about whose structure little is known, is probably a "spontaneous" polymer formed from the original resin acids by air oxidation and copolymerization. Autoxidation is possibly also involved in the formation of kerogen[32].

Microbiological decomposition undoubtedly also occurs in the upper layers of a sediment, but this can no longer be detected at a depth of a few meters. The free sulfur that is often present in sediments may be regarded as evidence of this process; the C_{12}—C_{18} iso- and anteiso acids *(1)* and *(2)* isolated from recent marine sediments may be assumed



to be residues of a bacterial organic material, since these compounds, which are rare elsewhere, are frequently found in present-day bacteria[33].

Arpino et al.[34] have detected long-chain methyl ketones containing odd numbers of carbon atoms as well as other long-chain compounds in a clay-rich limnic sediment from the Eocene (30% C) found at Bouxwiller (Alsace). These long-chain methyl ketones have not so far been found in the plant cuticle but have only been isolated from humous soils and peat[35]. They may be present in the sediment as a result of microbiological modification of fatty acids (β-oxidation followed by decarboxylation) or of *n*-alkanes (oxidation), such as has been found for compounds having lower molecular weights[36].

Microbiological decomposition processes of this type, the mechanism of which is largely unknown, are extremely important in the topmost layers of the sediments, and may play an important part in particular in the formation of kerogen.

6.2. Changes due to Physico-Chemical Effects in Early Diagenesis

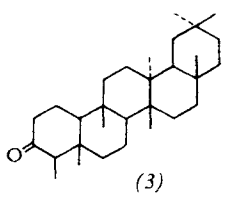
Important changes in the original organic material can be brought about by the acidic-basic and oxidizing-reducing conditions prevailing in the sediment. The retention of molecular structures is known to be endangered most by acids and oxidizing agents. In the presence of reducing agents, on the other hand, the molecular skeleton generally remains intact, though partial or complete hydrogenation or hydrogenolysis may occur. However, even compounds containing functional groups may remain unchanged under favorable sedimentation conditions. Two possibilities must therefore be considered for the origin of some compounds, such as hydrocarbons.

If the compounds found can be compared with biological precursors, *i.e.* particularly in the case of "biological markers", it should be possible to draw certain inferences concerning the geological conditions.

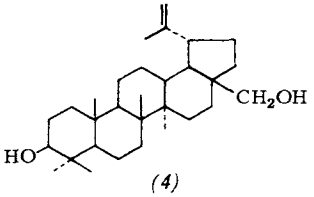
6.2.1. Unchanged Biogenic Substances in Sediments and Fossils

It first became possible to identify unchanged, relatively sensitive, biologically important molecules as well as degradation products in studies on lignite (*i.e.* a sediment that is very poor in inorganic matter). For example, the triterpenes friedelin *(3)* and betulin *(4)*, which are of wide occurrence in the plant kingdom, have been isolated from a Czech Miocene lignite (25 million years old)[37].

Our investigations on the organic material in the Eocene oil shale from Messel (near Darmstadt)[20] have shown that



(3)



(4)

besides the alkanes and fatty acids, very sensitive biogenic substances containing functional groups can also survive unchanged for more than 50 million years. The Messel oil shale[38], which is famous for its fossil flora and fauna, is a limnic sediment deposited in small continental basins, which has never been buried more than 200–300 m deep[39]. The samples investigated consist of a finely layered shale containing water, with about 30% of carbon and 35% of a clay fraction consisting almost exclusively of montmorillonite.

The first indication of the continental origin of the organic material is provided by the distribution of the *n*-alkanes, which shows a strong predominance of the compounds with odd numbers of carbon atoms (Fig. 4). This feature is characteristic of the cuticle paraffins of higher plants, as was shown in the example of *Equisetum* (Section 5).

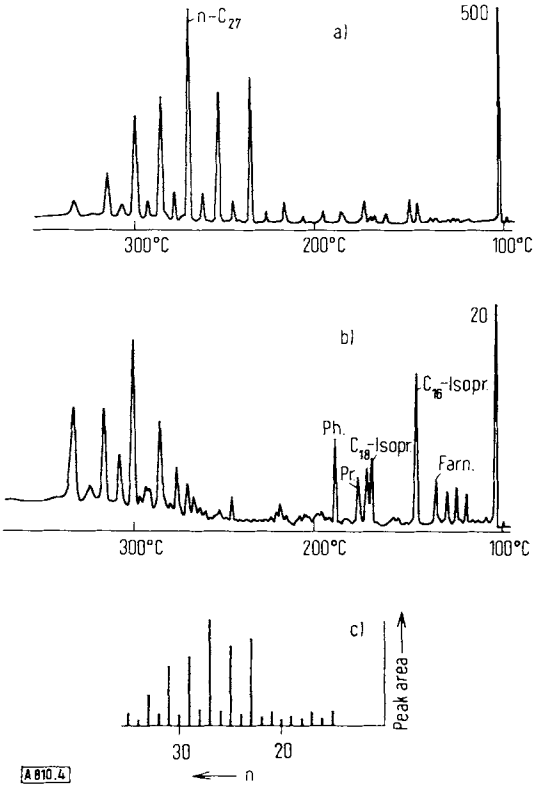
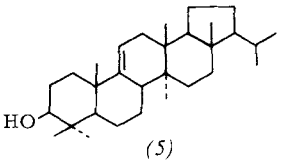


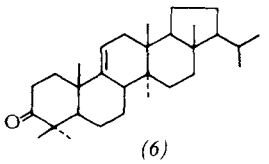
Fig. 4. Gas chromatograms of the saturated hydrocarbons of the Messel oil shale. (a) Total, (b) branches, (c) linear hydrocarbons. Column: 1.5% of SE30, 1,50 m. Pr. = pristane, Ph. = phytane, Farn. = farnesane, Isopr. = isoprenoid, n = number of C atoms. For the definition of isoprenoid see Section 6.2.3.

Further information is provided by the triterpene alcohol isoarborinol *(5)* and the ketone arborinone *(6)*, which occur together with other polycyclic alcohols and ketones in the Messel oil shale. A compound like isoarborinol is very susceptible to oxidation and reduction, as well as to attack by acids and heat. Its occurrence in the original form is indicative of mild conditions during diagenesis in the Messel sediments. It is not yet possible to establish the fossil plants in which these substances occur. The group of triterpenes of the arborane type was discovered fairly recently[40], and has so far been isolated only from tropical plants. Since the fossil flora found in the Messel oil shale is very closely related to the present-day plants of the

tropical regions[38,41], it should be possible to achieve a paleo-ecological approximation by studies on the organic compounds of certain sediments.



(5)



(6)

Extremely sensitive olefins and steroids from the Messel oil shale decompose rapidly in air after their isolation[42,43]. It is almost unbelievable that such substances could have survived in their original form in a sediment for millions of years, and suggests that the sediment is to some extent a sealed system.

The long-chain esters, which are extremely characteristic of plant cuticles, have been isolated from many lignites and coals[43]. They occur in the Messel oil shale and in the limnic sediments of Bouxwiller, and are undoubtedly unchanged biogenic substances[34,44].

Unesterified free long-chain alcohols with even numers of carbon atoms, which are also found in the cuticles of higher plants, have been detected in the Bouxwiller sediment[34]. Other free alcohols have been identified in several recent and earlier sediments[45].

6.2.2. Degraded Biogenic Substances in Sediments and Fossils

Blumer's investigations[28] on fossil crinoids (sea lilies) point to a correlation between the polyhydroxyquinoid pigments and the aromatic hydrocarbons that occur in the same fossil as reduction products of the pigments. These substances appear to form an oxido-reduction series (Fig. 5). Though most of the reactions, particularly the reduction of functional groups containing oxygen to alkyl groups, are probably irreversible under the geological conditions, a few reactions, such as hydrogenation and dehydrogenation, seem to proceed reversibly under certain sedimentation conditions.

These arguments are supported by the great similarity of the distributions (GC, MS) of the polycyclic alcohols and of the polycyclic ketones in the Messel oil shale, which point to a possible equilibrium between these two groups of compounds. However, it is not yet possible to say whether this is due to a true equilibrium or to incomplete irreversible reactions under geological conditions[42].

Pigments containing four pyrrole groups, which result from the dehydrogenation of chlorophyll or of hemin, occur in many sediments and petroleums as nickel and vanadyl complexes. In his investigations on porphyrins in the Swiss oil shale of Serpiano (Triassic, 200 million years old), *Blumer*[28] was able to explain a number of degradation reactions brought about by the geological environment. It can be seen from Figure 6 that complete reduction by "degradative decarboxylation" of the carboxyl group and cleavage of C—C bonds as described by *Cooper* and *Bray*[46] occur as well as decarboxylation.

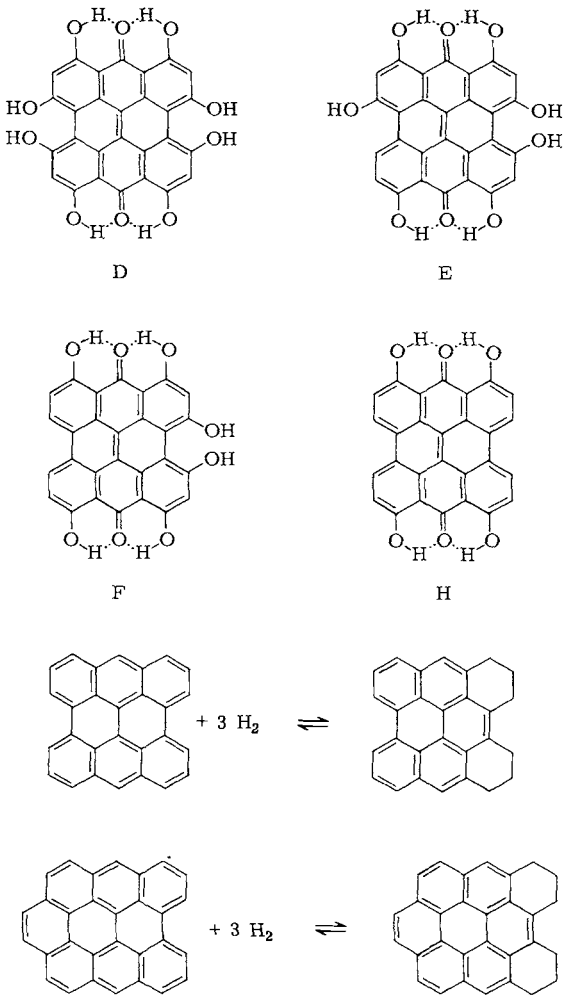
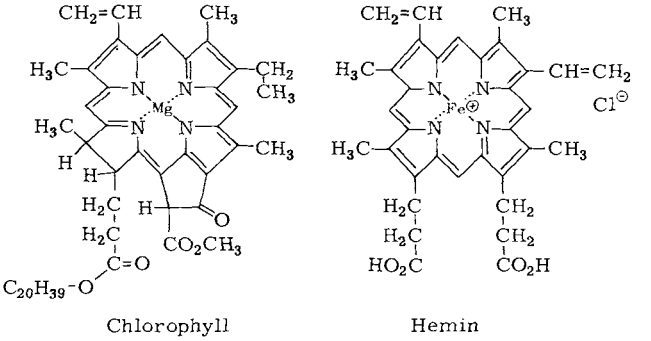


Fig. 5. Pigments (fringelites D, E, F, and H) and hydrocarbons from a fossil crinoid (sea lily) (after [28]).



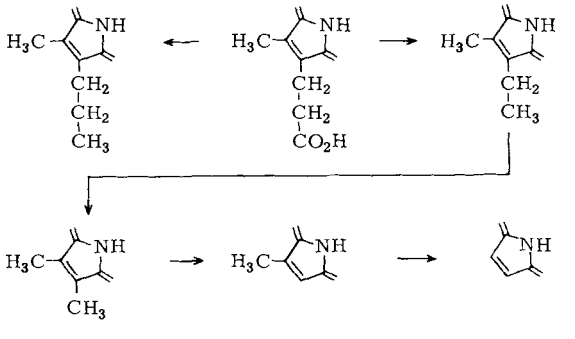


Fig. 6. Some diagenetic reactions of the pigments (after [28]).

Since the reduction of such a carboxyl group to a methyl group occurs in the laboratory only under very vigorous conditions, it is surprising that reactions of this kind take place in the sediment at low temperatures and in the presence of water. Some irreversible and possible reversible geochemical reactions detected in particular in the study of fossil pigments are listed in Table 3.

Table 3. Irreversible and reversible geochemical reactions (after [28]).

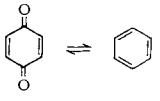
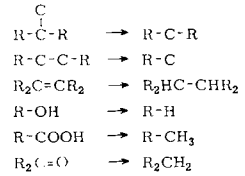
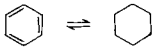
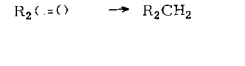
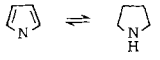
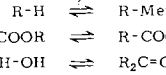
Irreversible processes	Reversible processes
R-COOH → R-H	
R-COOH → R-H + acids and hydrocarbons of low and of high molecular weight	
	
	
$R_2C{=}CR_2 \rightarrow R_2HC{-}CHR_2$	
R-OH → R-H	
R-COOH → $R{-}CH_3$	
$R_2C{=}O \rightarrow R_2CH_2$	$R{-}H \overset{?}{\rightleftharpoons}$ R-Metal
	R-COOR ⇌ R-COOH
	$R_2CH{-}OH \rightleftharpoons R_2C{=}O$

Figure 7 shows the composition of the alkanes from the extensively studied shale of the Green River formation, which is by far the most important oil shale reserve in the USA. This limnic sediment deposited in an inland sea is a finely layered shale containing about 25% of carbon, whose inorganic fraction is poor in clay but rich in carbonates.

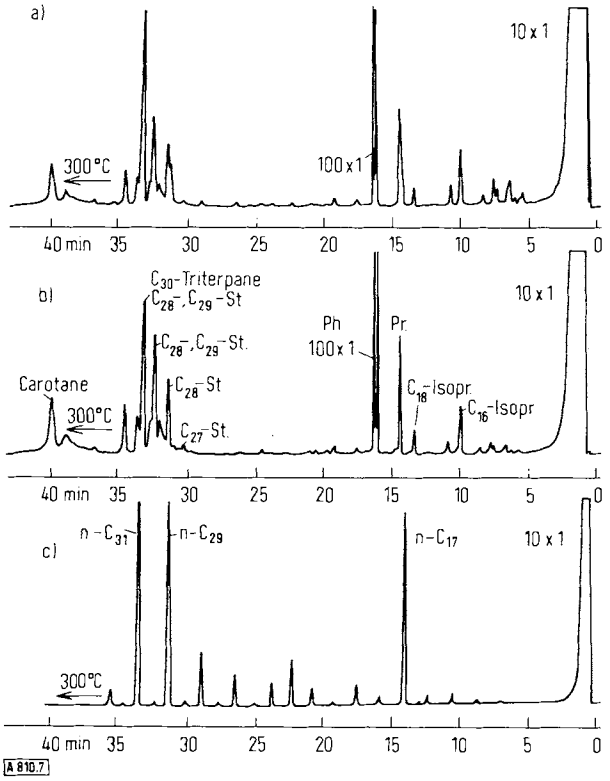
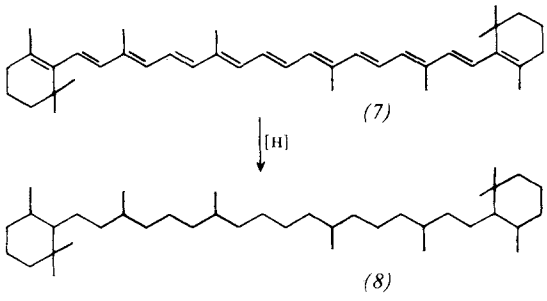
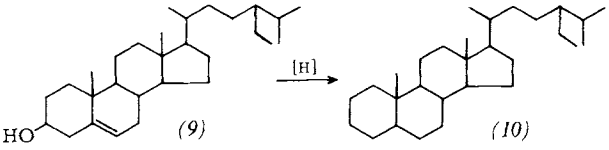


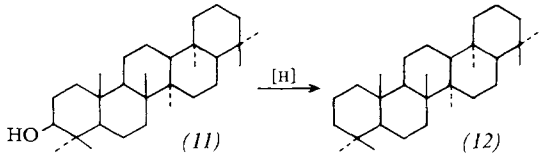
Fig. 7. Gas chromatogram of the saturated hydrocarbons of the Green River Shale. (a) Total, (b) branched and cyclic, (c) linear hydrocarbons (after [18]). Pr. = pristane, Ph. = phytane, St. = sterane, Isopr. = isoprenoid. For the definition of isoprenoid, see Section 6.2.3.

The compounds sitostane *(10)*, ergostane, cholestane, gammacerane *(12)*, and carotane *(8)* that occur in this shale[26, 47] are not present as biogenic substances in plants or animals, so far as is known. They were therefore most probably formed by reduction of the compounds β-sito-

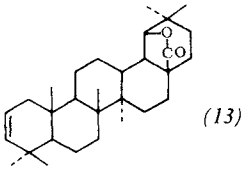


sterol *(9)*, ergosterol, cholesterol, gammacerin *(11)*, and β-carotene *(7)*, which occur widely in nature. Gammacerin has recently been detected in a protozoon.





Some petroleums also contain polycyclic compounds, which may be taken as evidence that not all of the organic material is of marine origin. Thus, *Barton et al.*[48] have detected the triterpene lactone *(13)* in an American petroleum; this compound may be regarded as a product of the acid-catalyzed degradation of the triterpene betulin *(4)*, which frequently occurs in the flora.

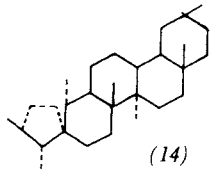


By capillary column gas chromatography and mass spectrometry, *Hills* and *Whitehead*[21] have isolated some polycyclic compounds, whose biological precursors are known in the present-day plant world in the form of alcohols, from optically active fractions of a Nigerian petroleum.

It may be assumed that such degradation reactions took place during earlier stages of diagenesis in the sediment before the migration in the petroleum formation.

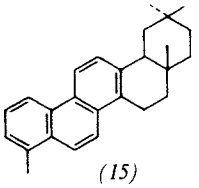
All these polycyclic, frequently saturated substances still contain enough information in their ring skeletons to serve as "biological markers" or even as "paleo-ecological markers". Their presence enables one to say whether the

organic material of a sediment is of marine or terrestrial, plant or animal origin. Such a classification could be made more precise if the distribution of all the oxygenated and unsaturated precursors in the present-day plants and animals were known. However, care is required since fundamental transformations are possible. For instance, a spirotriterpane has been isolated from a Nigerian petroleum [*(14)*, structure determined by X-ray crystallography]; such structures have not so far been detected in plants, and the compound in question is probably a rearrangement product formed by the catalytic action of clay[11].

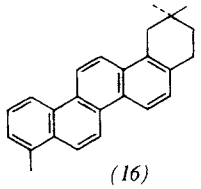


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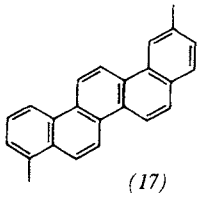
Partly dehydrogenated substances frequently also occur. These may be used as "biological" or "paleo-ecological labels" if their structures still contain sufficient information that points to biological precursors. Thus, *Jarolim et al.*[49]



(15)

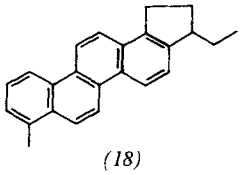


(16)

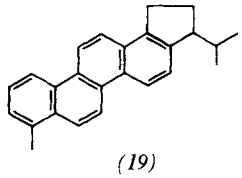


(17)

have isolated products of a dehydrogenation series of triterpene precursors [*(15)*, *(16)*, and *(17)*] from a Czech lignite. The compound *(17)* has also been found by *Carruthers* and *Watkin*[50] in an American petroleum. *Albrecht*[42] was able to identify small quantities of the dehydrogenated triterpenoid substances *(18)* and *(19)* in the Messel oil shale. It may be assumed that such compounds are formed in the sediment by disproportionation reactions.

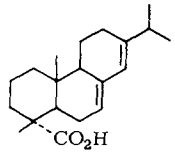


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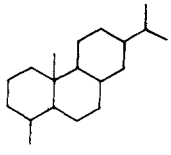


(19)

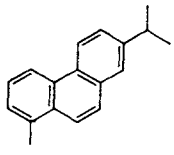
It is interesting to note that some compounds occur in hydrogenated forms and others in dehydrogenated forms in the same rock. Both types even occur together for some substances. Thus fichtelite *(22)* and retene *(21)*, which are undoubtedly formed from the same starting material [abietic acid *(20)*] by decarboxylation, and hydrogenation and dehydrogenation, respectively, have been isolated from a fossil wood[51]. Dehydroabietene *(23)*, another degradation product of abietic acid, occurs in large quantities (4.6%) in the soil of a Canadian pine forest[52], and dehydroabietic acid *(24)*, the simplest dehydrogenation product of abietic acid, has been found in the rosin lining the inside of the coffin of *Mary Ward*, a 16th Century English saint[53].



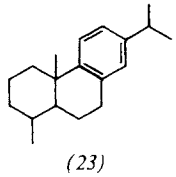
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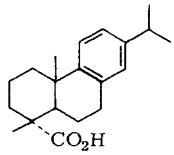
(21)



(22)



(23)



(24)

Little is known about the course of such degradation reactions of biogenic substances. It is not impossible that some of the reactions described were caused by microbiological processes.

6.2.3. Dual Origin of Some Groups of Compounds

"Dual origin" refers to the fact that a compound isolated from sediments or fossils was originally present both as such and as a precursor. Three groups that are of great biological significance have been selected as examples here. These are the long-chain isoprenoids and the linear alkanes and fatty acids.

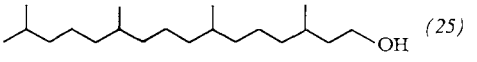
Isoprenoid compounds: The long-chain saturated isoprenoids have attracted special interest in recent years. These compounds occur in nearly all geological sources, such as petroleum[54], lignite[55], coal[56], oil shales[57], and other sediments[18], usually without functional groups, but also in the form of acids and alcohols. The isoprenoids are mainly between C_{15} (2,6,10-trimethyldodecane = farnesane) and C_{20} (2,6,10,14-tetramethylhexadecane = phytane), but with little or no C_{17} isoprenoid; they frequently account for the greater part of the branched alkane fraction (*e.g.* 3.4% of the total benzene extract from Green River shale)[57].

Traces of C_{17} isoprenoid have been detected for the first time in Antrim shale, a 265-million-year-old shale from Michigan, by *McCarthy* and *Calvin*[58]. This substance is also found in the deeper Upper Cretaceous sediments of the Douala Basin (Cameroon)[42].

The C_{21} isoprenoid (2,6,10,14-tetramethylheptadecane) is also present in several sediments[59]. *Han* and *Calvin*[60] even detected traces of C_{22}—C_{25} isoprenoids in a Californian petroleum (Bell Creek oil).

Saturated C_{14}—C_{22} isoprenoid acids can be isolated together with linear saturated acids in the free form from several sediments and petroleums[61]. *Murphy et al.*[62] re-

cently reported the presence of traces of C_{18} isoprenoid acid (6,10,14-trimethylpentadecanoic acid) in Green River shale. *Burlingame* and *Simoneit*[63] showed that most of the acids in Green River shale are in the form of the calcium salts.



(25)

Sever and *Parker*[45] have been able to determine traces of dihydrophytol *(25)* in many recent and some older sediments.

The long-chain isoprenoids, which are of widespread occurrence in living nature as unsaturated compounds, very rarely occur as saturated substances. Pristane (2,6,10,14-tetramethylpentadecane) and phytane have been found in some algae and bacteria[64]. However, pristane is a relatively important component in marine zooplankton, in which it occurs together with monoolefins having the same carbon skeleton (zamenes) and with phytadienes; it is also present in fish oils and in whale oil[28]. In zooplankton and in the oils, these compounds together with the isoprenoid acids are probably the end products of a metabolic degradation pathway of the phytol side chain of the phytoplankton chlorophyll in the marine nutritional chain.

A strong dominance of pristane in an "immature" (*i.e.* not too deeply buried) sediment could, according to these results, indicate that the organic material is of marine origin, and pristane could thus be a "paleo-ecological marker". *Blumer* and *Snyder*[65] found pristane, but not phytane, in two recent marine sediments. This compound is also by far the most common branched alkane in the upper, relatively little diagenetically changed layers of the Upper Cretaceous of the Douala Basin (Cameroon) (see Section 6.3)[66]. This is also so in the French marine oil shale of Créveney (Jurassic) (Fig. 8), which is 180 million years old, and has never been very deeply buried[67]. In immature sediments of nonmarine origin, as in the case of the Green River shale (Fig. 7) or the Messel oil shale (Figs. 4 and 9), on the other hand, phytane or the C_{16} isoprenoid predominates. However, these results are in need of confirmation from a large number of suitable sediments.

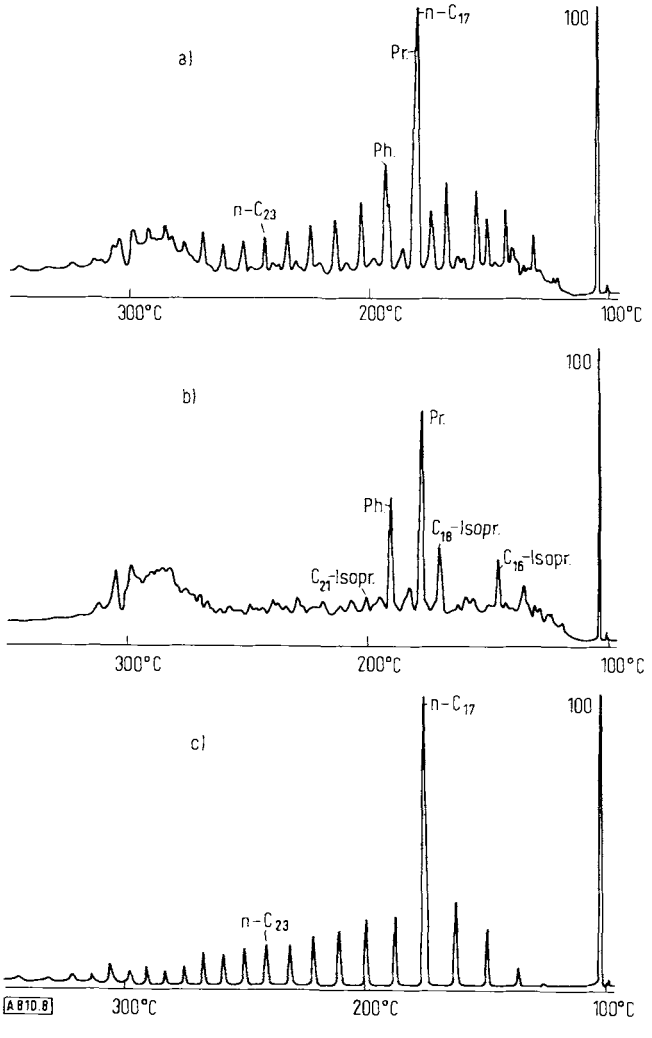


Fig. 8. Gas chromatogram of the saturated hydrocarbons of a marine oil shale (Créveney, Jurassic). (a) Total, (b) branched and cyclic, (c) linear hydrocarbons. For conditions and abbreviations, see legend to Fig. 4.

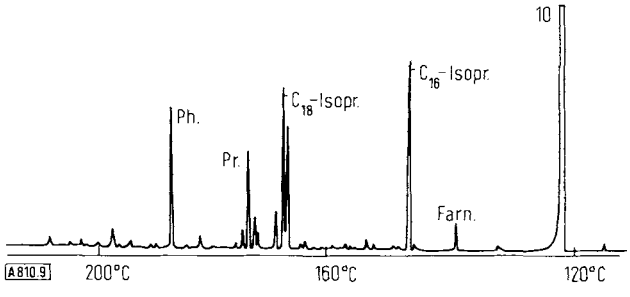
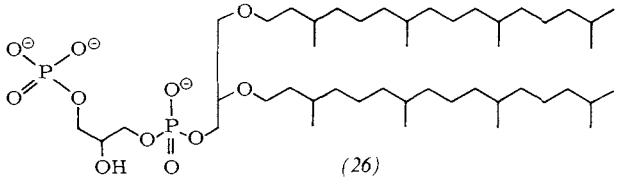


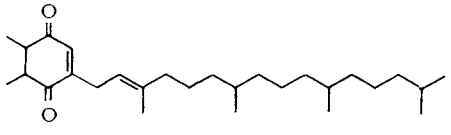
Fig. 9. Capillary column gas chromatogram of the low molecular weight branched alkanes of the Messel oil shale. Polyphenyl ether column 45 m × 0.25 mm.

Compounds with isoprenoid chains have been found in bacteria and algae[68], *e.g. (26)* in the halophilic bacteria *Halobacterium cutirubrum* and *(27)* in the fresh-water algae *Euglena gracilis*. However, chlorophyll is by far the most widely occurring compound with an isoprenoid side chain (Fig. 10); it may be assumed that a large proportion of the isoprenoids in fossils and sediments is derived from this substance through oxidation-reduction reactions, possibly also involving microbiological processes.

Phytane could be formed from phytol by hydrogenation and hydrogenolysis or by elimination of water and subsequent hydrogenation of the phytadiene. Reduction of



(26)



(27)

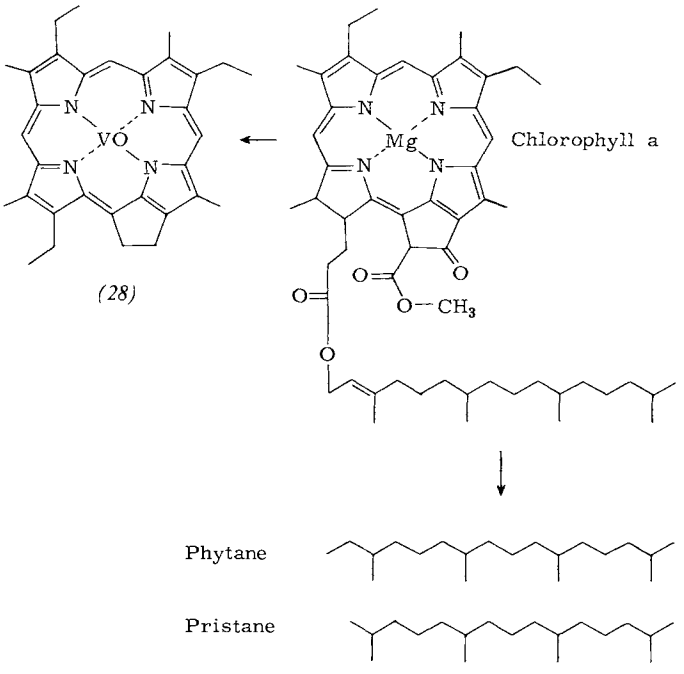


Fig. 10. Probable geochemical degradation reactions of chlorophyll with formation of vanadyldeoxyphylloerythroetioporphyrin *(28)*, phytane, and pristane.

phytol to dihydrophytol, which has been isolated from sediments, could lead after oxidation to phytanic acid, decarboxylation of which yields pristane. Isoprenoids with low molecular weights could then be formed by further "degradative decarboxylation" according to *Cooper* and *Bray*[47]. However, it is also possible that the hydrocarbons found are formed from the intermediate phytadienes and phytenes by cleavage of the CC double bonds and by reduction.

Isoprenoids in more deeply buried sediments may also be degradation products of kerogen or cracking products of the isoprenoid hydrocarbons (see Section 6.3).

n-Alkanes have been detected in nearly all sediments though sometimes only in small quantities. Like the isoprenoids, these compounds may be original biogenic substances or they may have been formed during diagenesis by reduction of molecules containing functional groups.

The *n*-alkanes can often be regarded as "paleo-ecological markers", particularly in immature sediments. Thus the predominance of *n*-alkanes with odd numbers of carbon atoms (between C_{23} and C_{35}) that is so characteristic of higher plants is found in terrestrial sediments, *e.g.* in Green River shale (Fig. 7) and in the Messel oil shale (Fig. 4), but also in many recent marine sediments, where they may serve as evidence of the supply of terrestrial organic material. This predominance is weak or absent in most marine organisms and in lower terrestrial plants[30,64b,69]; *n*-heptadecane is often the main component. The predominance of *n*-heptadecane is particularly pronounced in several immature marine sediments, *e.g.* in the Créveney oil shale (Fig. 8) and in samples of the topmost sediments of the Upper Cretaceous of the Douala Basin (see Fig. 14); between C_{23} and C_{35}, the alkanes with odd numbers of carbon atoms no longer predominate. The distribution in Green River shale probably points to a dual origin of the organic material of this sediment, which is partly derived from higher plants and partly from lower fresh-water plants.

Knoche et al.[70] have investigated the saturated hydrocarbons in a Lower Triassic fossil conifer, *Voltzia brongnarti*, that occurs in the variegated sandstone of the Vosges. Unlike the horse-tail mentioned in Section 5, these fossil remains, of which about 60% is made up of goethite (Fe_2O_3, H_2O), occur not in clay-rich inclusions but in the sandstone itself, as branches of varying thickness. The composition of the alkane fraction (3 mg from 2.6 kg of fossil) is remarkable, since it consists almost entirely of *n*-octacosane ($C_{28}H_{58}$). In view of the preference for alkanes with odd numbers of carbon atoms in the higher plants, this is probably a modification product. In the search for possible biological precursors, *Knoche et al.* analyzed the extracts for some conifers related to the species *Voltzia*, which is now extinct. The alcohol *n*-octacosanol, occurring in the leaf wax of *Taxodium distichum* Rich. and *Ginkgo biloba* L., is a possible precursor, since it could yield the saturated hydrocarbon on hydrogenolysis of the primary alcohol group in the sediment.

The slight preponderance of *n*-docosane ($C_{22}H_{46}$) in several sediments[71] could similarly be the result of reduction of docosanol. This compound is the main component *e.g.* of the alcohol fraction of Green River shale[45].

Decarboxylations, which have also been confirmed by *in-vitro* experiments[72], and complete reduction of the carboxyl groups of linear fatty acids[73] are further possibilities for "secondary" *n*-alkane formation in the sediments.

As a sediment sinks (see Section 6.3), the original distribution is partly masked by the dilution effect produced by the genesis of new hydrocarbons, and it is then more difficult to draw conclusions. Nevertheless, the compounds with odd numbers of carbon atoms may still predominate slightly in older, deeper sediments, and even in petroleums.

Linear fatty acids: These compounds may also be of "primary" or of "secondary" origin. They are often of great importance as "paleo-ecological markers". Thus the preponderance of linear saturated fatty acids with even numbers of carbon atoms between C_{22} and C_{32} in the Messel oil shale may be regarded with certainty as a contribution from the organic material of higher plants[44]. On the other hand, the fatty acids with even numbers of carbon atoms below C_{20} are usually most abundant in organisms of marine or lower terrestrial origin[74]. Thus tetradecanoic, palmitic, and stearic acids are the main components of the acid fraction in some recent marine sediments[33b]. There is often only a very slight preponderance of compounds with even numbers of carbon atoms in older, deeper deposits. Fatty acids with odd numbers of carbon atoms, among other compounds, appear to have been formed in these deposits during diagenesis. A correlation seems to exist between the distributions of *n*-alkanes and of *n*-carboxylic acids, particularly in older sediments[17]. However, this problem has not yet been finally settled.

A few words are appropriate at this point concerning the validity of the concept of "biological markers". The greater

part of the organic material that occurs in fossils and sediments is undoubtedly of biological origin. The few samples for which an abiogenic origin appears to be possible[75] (in Precambrian sediments and in meteorites) lack most of the "biological markers" mentioned in the above examples. Even the slight preponderance of *n*-alkanes with odd numbers of carbon atoms cannot be detected in these cases. Most is expected at present of the long-chain isoprenoids. However, some reservations are necessary here[76]. Polyisoprenoid chains can be synthesized stereospecifically by polymerization of isoprene with special catalysts, such as $Al(C_2H_5)_3$—VCl_3 (2:1)[77]; it is extremely unlikely, however, that such compounds have ever been available on earth as catalysts. On the other hand, a Fischer-Tropsch synthesis carried out by *Studier et al.*[78] with D_2 and with meteorite dust as the catalyst yielded, among other products, traces of deuterated C_9—C_{14} isoprenoids. Though no long-chain isoprenoids such as pristane and phytane were detected in this experiment, the result shows that abiogenic synthesis of certain long-chain isoprenoids over geological periods cannot be entirely ruled out.

McLean et al.[79] were able to separate diastereoisomers of esterified isoprenoid acids from Green River shale, and so to show that these acids are probably derived from chlorophyll. Separation of the diastereoisomers of phytane and detection of their optical activity could be an important step toward the solution of such problems.

6.3. Influence of Depth on the Organic Sediments

As a sediment becomes buried in a basin, it is subjected to a gradual rise in temperature and pressure. It loses most of its water, and both the inorganic material and the organic matter change. Laboratory experiments have shown that hydrocarbons can be produced by heating kerogen[3]. In most cases, however, experiments of this nature can give only a rough idea of reality, since they attempt to simulate the action of time, which plays a vital part in geology, by an excessive temperature rise.

A number of investigations have also been carried out on samples that have undergone natural diagenesis. Such experiments are of interest in connection with the problems of the origin and genesis of petroleum.

Louis and *Tissot*[80] have investigated the changes in the organic material of the Toarcian sediment layer (180 million years old) of the Paris Basin. This formation, which varies in its depth, appears on the surface at the edge of the basin, but is buried 2500 m down at the center. It thus provides samples of the same age, but from different depths. The ratio of alkanes to organic carbon begins to increase beyond a depth of 1400 m and at 60 °C. This increase, which signals the genesis of hydrocarbons, continues to the maximum depth of 2500 m (Fig. 11a).

Philippi[81] analyzed the hydrocarbons of various samples from the Californian basins of Los Angeles and Ventura. These samples reach, in the deepest layers, the Miocene deposits (12–15 million years old). Figure 11b shows a very pronounced increase in the hydrocarbon concentration in the Los Angeles basin at a depth of 2400 m and at 115 °C, continuing to 3500 m. The increase is accompanied by a change in the alkane distribution. The strong preponderance of compounds with odd numbers of carbon atoms between C_{27} and C_{33} above 2400 m, which is characteristic of the terrestrial influence, begins to decrease beyond this depth, and is insignificant beyond 3300 m, since the original hydrocarbons are now diluted with those formed later.

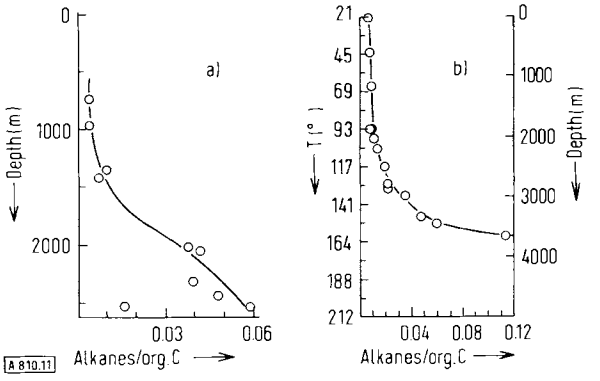


Fig. 11. Variation of the ratio of alkanes to organic carbon (org. C) with depth (a) in the Toarcian formation of the Paris Basin (after [80]), (b) in the Los Angeles Basin (after [81]).

We have investigated the hydrocarbons present in samples from the Upper Cretaceous sediments (80 million years old) of the Douala Basin (Logbaba, Cameroon)[66, 42]. Important characteristics of this series are shown by the geological history of the basin and by an accurate analysis of the inorganic material[82]. Because of the depth of the sedimentary series (4000 m), high temperatures (150 °C) and pressures (650 atm) are reached in the deepest layers. This geochemically homogeneous series, which was formed in a relatively short time (about 15 million years), consists of nearly horizontal sediment layers that are very rich in clay, sometimes interspersed with small sandstone lenses. The diagenesis of the clay fraction has been studied in great detail, and points to a gradual change in the clay minerals. In particular, the montmorillonite that mostly occurs in the upper layers changes beyond 1200 m into a montmorillonite-illite interstratified clay; this finally gives way, in the deepest part of the basin (3500 m), to illite, a non-swelling clay[82]. It was therefore assumed that this homogeneous series would be particularly suitable for studies on

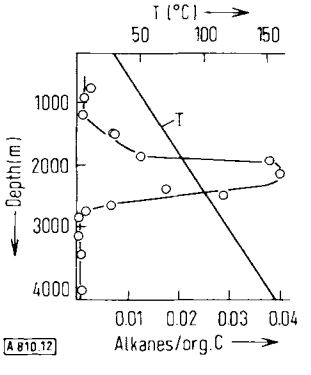


Fig. 12. Variation of the ratio of alkanes to organic carbon (org. C) with depth in the Upper Cretaceous sediments of the Douala Basin (Cameroon).

the organic material, and that changes could be interpreted as a consequence of diagenesis due to depth.

Figure 12 shows the depth variation of the ratio of alkanes to organic carbon (the total content of organic carbon in these sediments is 1–2%). A significant increase in the ratio at 1200 m confirms the results reported by *Louis* and *Tissot* and by *Philippi*. However, a correlation is also found between time and genesis temperature. In geologically younger basins such as that of Los Angeles (15 million years old), the genesis processes require much higher temperatures (115 °C) than in the older basins of Douala (80 million years old, 65 °C) and of Paris (180 million years old, 60 °C). The pressure appears to be of minor importance. Time and temperature are in fact to some extent interchangeable factors.

Because of the great depth and age of the Douala sediment series, other phenomena are also observed. At 2200 m (95 °C) the ratio of alkanes to organic carbon, after passing through a maximum, begins to decrease once more, and falls off to low values beyond 2800 m. This result, which is caused particularly by thermal effects, is undoubtedly the outcome of diagenesis due to depth, since the change in the ratio of alkanes to organic carbon is accompanied by a very regular variation of the distributions of the *n*-alkanes and of the branched alkanes (Figs. 13 and 14). C_R/C_T (carbon ratio), *i.e.* the ratio of the organic carbon that is non-volatile at 900 °C under nitrogen (C_R) to the total organic carbon (C_T) of the kerogen[83], increases steadily with depth, pointing to a gradual transition of the organic

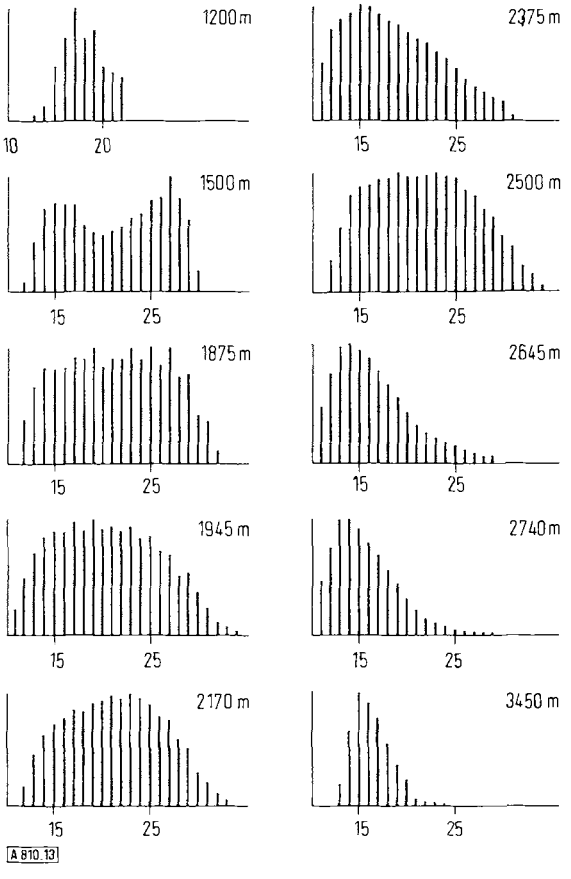


Fig. 13. Variation of the distribution of *n*-alkanes with depth in the Upper Cretaceous sediments of the Douala Basin (Cameroon). Ordinate: Signal area; abscissa: number of carbon atoms.

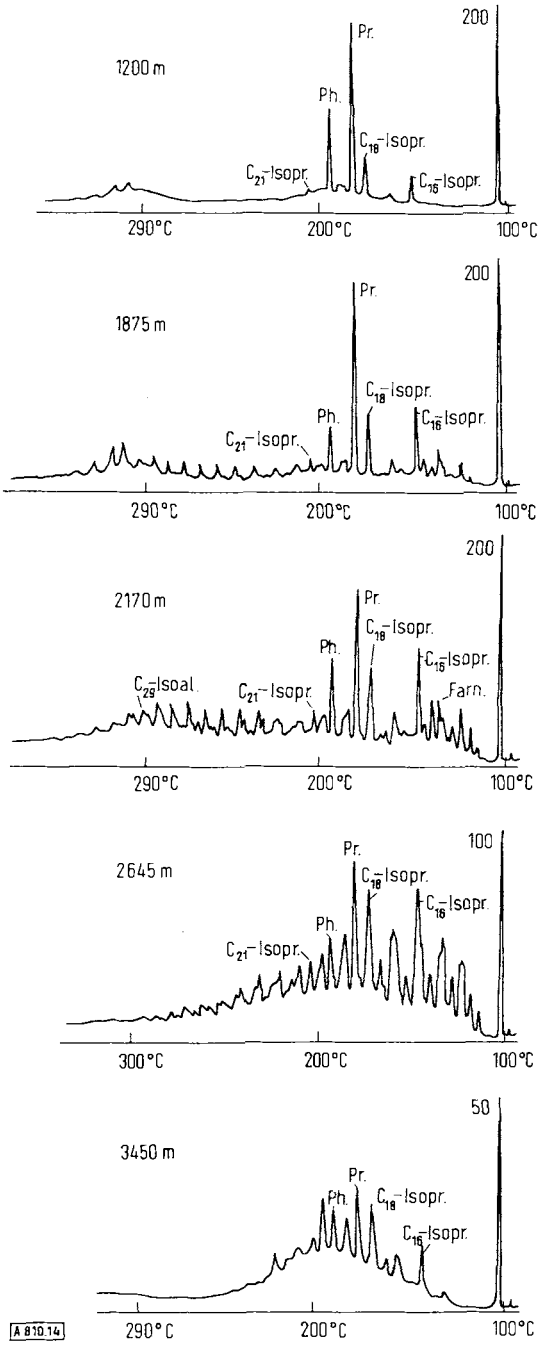


Fig. 14. Variation of the distribution of branched alkanes with depth in the Upper Cretaceous sediments of the Douala Basin (Cameroon). Gas chromatograms recorded under the same conditions as for Fig. 4; for abbreviations see legend to Fig. 7. Isoal. = isoalkane.

material into graphite[84]. The homogeneity of the original organic material is confirmed by the fact that the isoprenoids occur in practically the same proportions, irrespective of depth[85]; the pronounced dominance of pristane and the distribution of the *n*-alkanes in the uppermost sediment deposits point to a material of marine origin. Finally, the main results of the investigation have been confirmed by heating experiments carried out in the laboratory on the uppermost samples[42]. The newly formed hydrocarbons result partly from the removal of functional groups from the soluble fraction of the organic material and partly from the cleavage of bonds in the kerogen. Beyond 2200 m in the West African series of the Douala Basin, C—C bonds are also frequently cracked by the

higher temperature under the catalytic action of the clay. This is shown by the disappearance of high molecular weight in favor of low molecular weight compounds and the gradual appearance of an isomer mixture, which cannot be resolved by gas chromatography, in the series of branched alkanes. It is known that model reactions with dry clays as catalysts proceed by a carbonium ion mechanism[72], which favors branched compounds[72].

Such investigations are particularly interesting in connection with petroleum problems. Petroleum is probably formed in the finely divided organic material of the sedimentary rocks, which moves into porous reservoir rocks such as carbonates or sandstones during a migration process, where the oil phase separates from the water phase. It is generally assumed that this "primary" migration is usually restricted to short distances[86]. Fig. 15 shows a

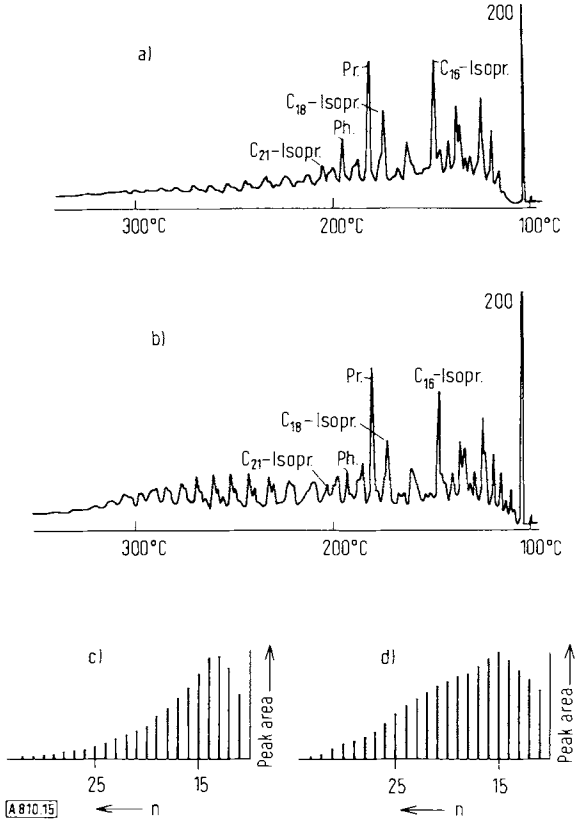


Fig. 15. Comparison of the alkane distributions of a petroleum and of a rock sample from under the reservoir rock (Upper Cretaceous of the Douala Basin, Cameroon). (a) Petroleum, branched alkanes, (b) rock, branched alkanes, (c) petroleum, *n*-alkanes, (d) rock, *n*-alkanes. For abbreviations, see legend to Fig. 7. n = number of carbon atoms.

comparison of the alkanes of a petroleum found in a sandstone lens at a depth of 2360 m in the sediment series of the Douala Basin with those of a lower-lying deposit (2364 m) whose organic material may have contributed to the formation of the oil. The very similar isoprenoid distributions confirm that the oil is probably related to the organic material of the neighboring sediment. The concentrations of higher *n*-alkanes and isoalkanes are lower in the oil than in the sediment, in agreement with the more recent migration theories, such as *Baker*'s micelle solubility theory[87] or the frontal chromatography process postulated by *Meinschein et al.*[88].

7. Investigations on Precambrian Sediments

According to *Darwin*'s continuity principle, a chemical evolution must have preceded biological evolution on earth. The transition from chemical to biological development could, *e.g.* according to *Oparin*'s theory[89], have occurred by formation of membranes around small droplets of organic substances, and would have led at a very early period to important changes in the composition of the organic material[90]. The investigations on Precambrian rocks were originally carried out in the hope of detecting such changes in the organic material of the sediments.

The ages of the Precambrian sediments investigated so far, which can be determined with good accuracy by isotope dating methods, range from one billion years for the North American Nonesuch shale to more than three billion years for the Fig Tree and for the Onverwacht series of South Africa. For comparison, the age of the earth is estimated to be about 4.6 billion years.

Only very few morphologically well-determined fossils from the period before the Cambrian are known. However, some microfossils, which correspond to present-day microalgae and bacteria, can be detected in Precambrian sediments[91]. Since it is often very difficult to determine the geological history of such old rocks, contamination with younger organic material, *e.g.* with younger petroleums, is one of the principal problems in the investigation of Precambrian deposits. Depending on the source of the organic material, the frequently used $^{12}C/^{13}C$ determinations show differences that, though small, can be easily measured with modern mass-spectrometric methods[92], and can be useful in the present case, since the $^{12}C/^{13}C$ ratio of the soluble fraction in most younger sediments is practically the same as that of the kerogen. If the kerogen is assumed to be an original polymeric material that cannot migrate, it can be shown by this method that some Precambrian sediments have probably been contaminated[16]. However, it is not certain that the isotope ratio has not been altered by external influences[90,93].

n-Alkanes and isoprenoids[94], as well as traces of fatty acids[95], porphyrins[96], and amino acids[97] have been detected in the small (but frequently investigated) soluble extracts. The kerogen fraction is very similar to that of younger sediments[6].

Though no transition from chemical to biological evolution has been found so far in the investigations on Precambrian sediments, it has been shown that biological material very probably existed on earth more than three billion years ago. Any transition from chemical to biological development must therefore have occurred even before this time, very soon after the formation of our planet.

8. Extraterrestrial Rock Samples

The investigations on extraterrestrial samples have so far been of interest particularly in connection with the possibility of extraterrestrial life. If such life had ever existed, it could also have been brought to earth. Some authors

believe that this is entirely possible, since the already complex biological processes detected in the older Precambrian sediments leave relatively little time for a chemical evolution[98].

Hayes has discussed this topic very critically[99]. Many of the extraterrestrial samples investigated are carbonaceous chondrites whose carbon contents are similar to those of terrestrial sediments; *n*-alkanes and the isoprenoids pristane and phytane have been detected in these meteorite samples[100]. Traces of aromatic compounds and biological compounds such as porphyrins, heterocyclic bases, and amino acids have also been found.

The impurities are again the main problem in such analyses. The difficulty here is not the determination of contamination, which can often be recognized by blank tests[101], but rather the impurities due to contact with the soil of the earth and in many cases to the long storage in museums (100 years in the case of the famous Orgueil meteorite). "Biological markers", the presence of which normally allows far-reaching conclusions to be drawn, can therefore not be used for the detection of extraterrestrial life. It is not impossible that part of the organic material in these samples was formed abiogenically *in situ*, since many substances identified in the meteorites can be synthesized abiogenically in the laboratory from simple organic and inorganic starting materials under the conditions of the primeval terrestrial atmosphere[99,102].

The analysis of the Pueblito-de-Allende meteorite, which landed in Mexico in February 1969, has led to a very remarkable result[103]. The determinations carried out in early March 1969 with a coupled apparatus for capillary column gas chromatography and mass spectrometry have shown that the soluble organic material is confined to the outermost layers of the meteorite, and no soluble substances can be detected in the interior. The organic material of the meteorite's crust, which is very similar to that of other meteorites, contains traces of *n*-alkanes and isoprenoids as well as saturated and unsaturated carboxylic acids.

This analysis thus shows that such samples very quickly become "contaminated"; it thus casts doubt on many earlier results, and shows the care that is necessary in studies in this field. It is possible that further help could be provided by an accurate analysis of the insoluble organic material in such samples[104].

The moon rock samples brought to earth by the Apollo expeditions have been analyzed with extreme precautions[105]. The first results indicate that these rocks contain only very small quantities, mostly in the contamination range, of organic material[106].

9. Kerogen

Kerogen is the name given to the insoluble polymeric organic part of the sediments. There is not just one kerogen, but many types. A rough classification by *Forsman* and *Hunt*[107] distinguishes between a coaly type and a non-coaly type of kerogen. Geomicrobiological studies have shown that at least part of the kerogen consists of various microbiological remains.

Though kerogen is the most abundant form of organic material on earth, very little is known about its structure or about its structural elements. As was mentioned in Section 6.3, it is the source of a substantial proportion of the hydrocarbons in the more deeply buried sediments, and hence also a large proportion of the petroleum. Hydrocarbons almost identical with those of petroleum have been prepared in the oil shale industry by heating kerogen to high temperatures. Kerogen is therefore a potential source of hydrocarbons.

Various attempts have been made to explain the formation of kerogen, which must occur in the early stages of sedimentation. According to *Abelson*[32], the cell membranes could change after the death of the plankton. The oxygen present may come into contact with reactive substances during the very slow sinking of such microscopic units. The formation of very reactive peroxides would then lead, as in the drying of linseed oil, to chain linkage. *Brooks* and *Shaw*[108] report a certain similarity between kerogen and sporopollenin, a component of the cell walls of pollen and spores. This polymer, which contains carotene esters among other compounds, yields substances similar to the kerogen of some sediments on oxidation. However, the problem is not that simple, since simple molecules also appear to be bound to the kerogen either chemically or as inclusions. *Blumer* and *Snyder*[109], for example, have shown that porphyrins are incorporated in the high molecular weight asphaltenes of the Swiss oil shale of Serpiano; such inclusions are undoubtedly also present in some way in the kerogen, as has been shown by the extraction of porphyrins by heating the kerogen of a recent sediment[110].

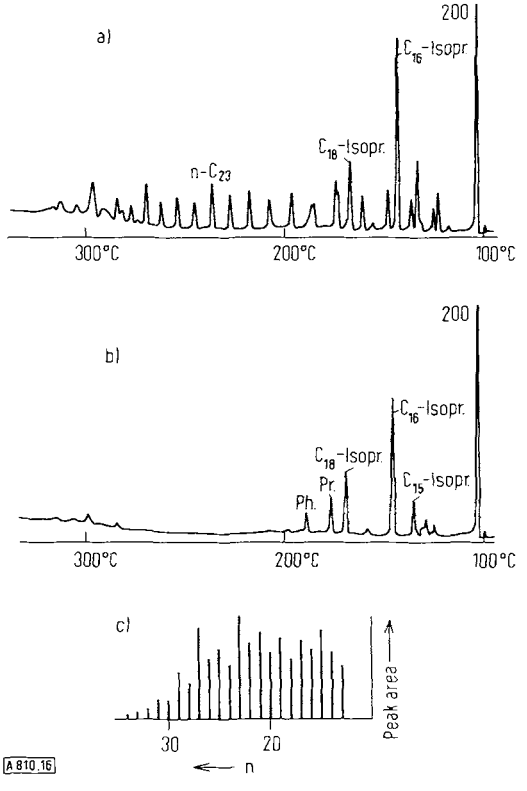


Fig. 16. Gas chromatogram of the alkanes formed by thermal degradation (40 h, 200 °C, under N_2) of the kerogen from the Messel oil shale. (a) Total, (b) branched and cyclic, (c) linear alkanes. For abbreviations see legend to Fig. 7. *n* = number of carbon atoms.

Numerous investigations have been carried out on the kerogen of Green River shale (65 %C) by thermal and chemical degradation[111]. *Burlingame* and *Simoneit*[112] managed to bring it into solution by oxidation for 48 hours with CrO_3. It was shown by mass spectrometry and gas chromatography that the main products are long-chain and isoprenoid acids. Even earlier, *Douglas et al.*[113] detected *n*-alkanes, olefins, and isoprenoids on thermal degradation of this kerogen. Hydrogenolysis at high temperatures, a procedure frequently used in the oil shale and coal industries, also brought 90 % of Green River shale into solution and led, *inter alia*, to the formation of saturated hydrocarbons with a strong preponderance of isoprenoids, particularly pristane[114].

The kerogen of the Messel oil shale (60 %C, 7 %H, 1.5 %N) yields long-chain *n*-alkanes on thermal degradation; when lower temperatures are used, a preponderance of alkanes with odd numbers of carbon atoms can be detected[39b]. With moderate heating (200 °C, 40 hours under N_2), in addition to *n*-paraffins, branched saturated hydrocarbons consisting exclusively of isoprenoids are also formed[42] (Fig. 16).

According to these preliminary results, the kerogen of this oil shale appears to be a polycondensed material with long straight and isoprenoid chains.

10. Conclusion

Investigations using the latest analytical methods have extended and deepened our knowledge of the composition and origin of the finely divided organic material of sediments and fossils. Because of the small quantities of organic substance, strict precautions are often necessary to avoid contamination in these studies.

The occurrence of original or degraded biological compounds in sediments and fossils shows that the organic material from these geological sources, with few exceptions, is of biological origin.

These "biological markers" can in many cases be used as "paleo-ecological criteria", since they allow the deduction of the origin of the organic substance with great certainty, and possibly its classification. They also provide valuable information about important degradation reactions of the biological material in the geological environment. In the topmost layers of the sediments, these processes are probably due to the action of microorganisms and oxidizing-reducing and acid-base effects of the environment. A better knowledge of the degradation mechanisms would be very welcome. As a sediment sinks in a basin, it is gradually exposed to rising temperatures and higher pressures. At a depth and temperature that depend on the age and lithology of the basin, bonds are broken in the soluble and insoluble organic fractions of the rock, with formation of new hydrocarbons, which can also be broken down later.

Petroleum comes from the finely divided organic material of sedimentary rocks, which collects in porous reservoir rocks during migration processes.

The biological processes have probably remained unchanged since the Precambrian. The presence of "biological markers" in the oldest sediments of the earth indicate, with a probability that borders on certainty, that life began more than three billion years ago, *i.e.*, geologically speaking, relatively soon after the formation of the earth. "Biological markers" in extraterrestrial rocks have also been closely examined in an effort to detect the existence of life outside the earth. However, no definite answer to this question can be given as yet.

Kerogen forms the greater part of the organic material in the sediments, and is thus the most general form of organic material on earth. Unchanged kerogen is a complicated polymer containing straight and isoprenoid chains, probably condensed, *e.g.* by ester and ether bridges.

When kerogen is heated, it undergoes degradation reactions that lead to new hydrocarbons. A better knowledge of its structure could help to explain its origin and the manner in which it was formed. This might lead to a better understanding of the hydrocarbon genesis that takes place during the sinking of sediments.

The arrangement of the organic and of the inorganic material in the sediments is also of great importance. It is interesting to contemplate how far the changes in the organic and inorganic materials during sedimentation are coupled.

Finally, the methods described here could also be useful in fields such as oceanography, soil research, and environmental science.

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Bond Character of β-Diketone Metal Chelates

By Bodo Bock, Karsten Flatau, Helmut Junge, Manfred Kuhr, and Hans Musso[*]

The vibrational spectra of molecules labeled with ^{2}H, ^{13}C, and ^{18}O show that delocalization of double and single bonds in the six-membered ring is complete in all the metal chelates investigated of 2,4-pentanedione (acetylacetone), but not in 2,4-pentanedione itself. Mercury, on the other hand, is bonded to the central C atom of the ligands. The NMR spectra of the metal chelates of 3-mesityl-2,4-pentanedione and 3-anthryl-2,4-pentanedione show that the chelate rings have no magnetic anisotropy comparable with that of benzene. A critical appraisal is made of the questions whether it is at all justifiable to attribute any "aromatic character" to such molecules and why all comparisons with the chemical reactivity of benzene have so far led to controversial conclusions concerning the character of the bonding in the metal chelates of 2,4-pentanedione.

1. Introduction

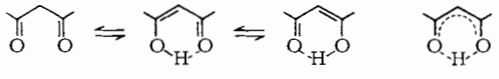
At various stages of its development the concept of aromatic character has stimulated chemists to compare unsaturated ring systems that had either been known for a long time, or specifically prepared for this purpose, with benzene. Although one is attracted by the formal similarity and the desire to approach the ideal of this state, more or less pronounced differences in the chemical and physical properties are found in practice.

To cope with this situation, various qualified expressions such as benzenoid and nonbenzenoid aromatic systems, heteroaromatic systems, quasiaromatic and pseudoaromatic systems, nonclassical aromatic systems, and anti-

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aromatic systems[1] were introduced. Alternatively, the aromaticity of a system is sometimes expressed in percentages[2]. Whether or not these terms are rigorously defined and based on theory, or are universally used and unambiguously understood, it is certainly of interest to know the experimental methods used in attempts to answer questions of bonding in such a molecule, as well as the results. The methods providing a relatively clear picture in the case of 2,4-pentanedione (acetylacetone) and its metal chelates will be described here.

The equilibrium between the keto and enol form of pentanedione [*(1)* and *(2)*] is established so slowly at room temperature that the two forms can be easily detected in each other's presence by their vibrational and NMR spectra. However, the two methyl groups of the enol form *(2)* give only *one* sharp signal in the ^{1}H-NMR spectrum, though their environments are different in the usual notation *(2)*[3], and it is very unlikely that the signals coincide by accident. Either the interconversion of the two tautomers *(2a)* and *(2b)*, which have equal energies, is very fast even at low temperatures (double minimum in the energy profile, Fig. 1) or the molecule has a symmetrical



(1) *(2a)* *(2b)* *(3)*

structure *(3)* in which the bonds between the acidic proton and the two oxygen atoms are of exactly the same length (only one broad minimum in the energy profile, Fig. 1).

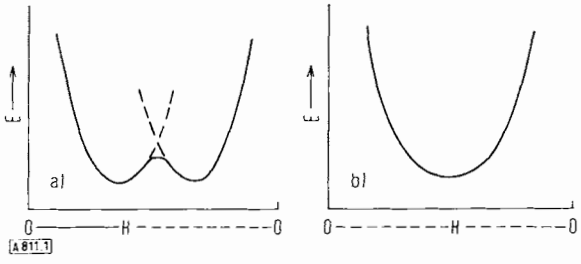
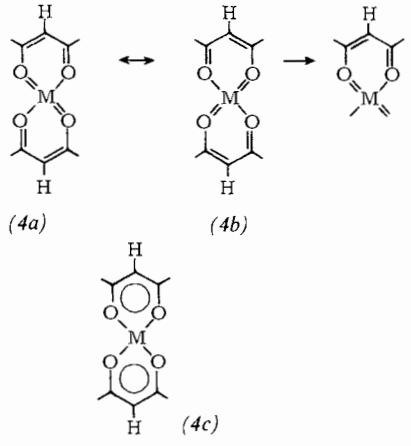


Fig. 1. Energy profile for (a) unsymmetrical and (b) symmetrical hydrogen bonds.

2,4-Pentanedione reacts with many metal ions to form complexes[4]. Those with chromium, cobalt, and rhodium are so stable that the central H atom on the chelate ring can be substituted as in benzene. They can be halogenated with *N*-bromosuccinimide or iodine chloride, acylated with acetic anhydride and boron trifluoride, formylated with phosphorus oxide chloride and dimethylformamide, converted into thiocyanates with dithiocyanogen and into thioethers with sulfenyl chlorides. Furthermore, they can be chloromethylated with chloromethyl ether, and nitrated with copper nitrate in acetic anhydride. The nitro compound can be reduced to amine; this gives a stable diazonium salt, which couples with β-naphthol, can be converted into the OH compound by heating, is reduced by ethanol, and can even be converted into the fluoro compound under the conditions of the Balz-Schiemann reaction[5].

Calvin[4] first tried to explain the stability of these chelates by a benzenoid resonance and represented it using resonance structures *(4a)*↔*(4b)* analogous to those used for benzene, the prototype aromatic compound. The similar-

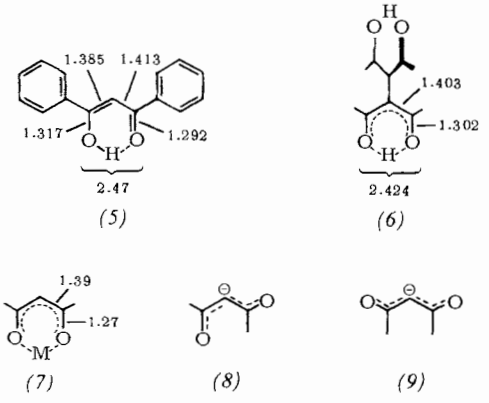


(4a) *(4b)* *(4c)*

ity of their behavior to that of the benzene ring in electrophilic aromatic substitutions led *e.g. Collman*[5] and *Bayer*[6] to attribute an aromatic, quasiaromatic, and pseudoaromatic character [see *(4c)*] to these compounds, and experimental results repeatedly appear which seem to confirm these conclusions[7].

2. Structure of 2,4-Pentanedione and Its Metal Chelates

In the keto form *(1)* of pentanedione, the acetyl groups can rotate about the bond to the central C atom, whereas the enol form is fixed in the planar *cis* structure *(2)* by the hydrogen bond. So far as is known, no attempt has been made to establish the position of the proton between the O atoms in the enol form by X-ray analysis or neutron diffraction. The electron diffraction in the gas phase at about 100 °C appears to be compatible with the symmetrical position *(3)*[8], but the radial distribution curve cannot be interpreted completely and conclusively with respect to the exact position of the light hydrogen atoms[9]. In the case of 1,3-phenyl-1,3-propanedione *(5)*, the X-ray structure in the crystal shows different lengths for the C—O and C—C bonds[10], whereas it has been reported that the proton in the crystal of tetraacetylethane *(6)* is probably



(5) *(6)* *(7)* *(8)* *(9)*

situated exactly midway between the O atoms[11]. Earlier structural analyses on metal chelates of 2,4-pentanedione show that, *e.g.* in the case of Cu, the lengths of the C—O and C—C bonds are slightly different[12], whereas the majority of recent investigations on many chelates of 2,4-pentanedione with a wide variety of metals (Mn, Zn, Cu, Ni, Cr, Al, Co, VO, Zr, Fe, Be, Ce[13], Co[14], Rh[15], Ni[16], Mn[17], Ce[18]) indicate a symmetrical electron distribution in the chelate ring; these investigations lead to the average values given in *(7)* for the C—O and C—C distances[13].

Slight deviations of the ligands from C_{2v} symmetry are rare (Zn[19], Fe[20], U[21], Cu[22]), and may be due to experimental errors, the particular arrangement in the crystal, or Jahn-Teller distortion[22]. The vibrational spectra indicate that the free anion prefers *trans* conformations *(8)* and *(9)* in solvents in which the complexes dissociate[23].

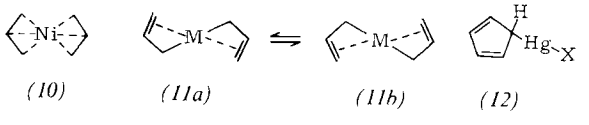
X-ray analysis, however, suffers from the following drawbacks in connection with this question:

1) The result refers to the crystal, in which the structure may be different from that in solution or in the gaseous state, owing to interaction with the neighboring molecules in the lattice.

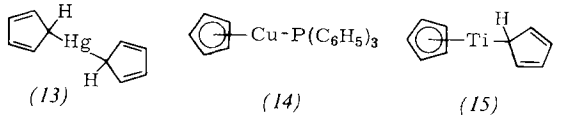
2) It is extremely difficult to decide whether the ligands are truly symmetrical or whether they deviate slightly from C_{2v} symmetry, irrespective of whether they have a regular alternating arrangement, are randomly distributed, or are in a rapid equilibrium.

3) The X-ray analysis yields only distances, and provides no direct information as to whether the conjugation in the chelate ring passes cyclically through the metal ion, though the average C—C distance is 1.39 Å, as in benzene.

This problem of double or single minimum, which has been discussed here for 2,4-pentanedione, also arises with



(10) *(11a)* *(11b)* *(12)*



(13) *(14)* *(15)*

many other molecules, and is constantly being discussed in the literature, *e.g.* in connection with the carboxylate ion[24], nonclassical carbonium ions[25], and σ- and π-allyl metal complexes, where both cases appear to occur, depending on the central atom and the ligand. Allyl residues are bonded symmetrically to Ni and Pd *(10)*[26], and unsymmetrically to Rh and Ru; phosphanes or arsanes as additional ligands can favor the interchange in the allyl residue *via* equilibria between σ and π bonds [*(11a)*⇌*(11b)*][27]. Cyclopentadiene is σ-bonded to mercury halides and mercury as in *(12)* and *(13)*[28–31], and a fast equilibrium, which is catalyzed by traces of mercury salts[31], occurs between all five C atoms, and may give an incorrect impression of a symmetrical *pentahapto* bond, *e.g.* in NMR studies. With other metals, *e.g.* in cyclopentadienyltriphenylphosphanecopper *(14)*, such a bond has been verified by IR[32] and X-ray analysis[33]. In comparable titanium compounds, the σ- and *pentahapto*-π types appear to occur together at the same central atom *(15)* and are in rapid equilibrium[34].

If NMR spectroscopy responds too slowly to detect the tautomers or valence-isomeric structures separately, as in the case of 2,4-pentanedione, vibrational spectroscopy is more promising. Structures with lifetimes of down to 10^{-12} s should still be recognizable in the region of C—C, C—O, and O—H stretching vibrations. It is only when the energy barrier between the tautomers *(2a)* and *(2b)* (Fig. 1) decreases to the order of magnitude of the vibrational quanta that band broadening must be expected. If the energy barrier is lower than the first vibrational level, it is no longer meaningful, in terms of vibrational spectra, to discuss different structures, since then these structures are simply vibrational amplitudes of the symmetrical structure. In cases where a proton oscillates between two oxygen atoms, as in the enol form of pentanedione, the frequency for small O—O distances, because of the tunnel effect[35], can be as high as 10^{11}, and thus approach the time resolution limit of vibrational spectroscopy; however, electronic spectra may then provide further information (see Section 6[100, 102]).

3. Analysis of the Vibrational Spectra

To obtain information about the symmetry of a molecule from the vibrational spectrum, one must first assign all the bands. When we began our studies, no unambiguous assignment of the bands in the IR spectra of copper bis-(pentanedionate) (Fig. 2) and other chelates of β-diketones was to be found in the literature. We shall first discuss only the first four strong bands at 1578, 1527, 1397, and 1281 cm^{-1}.

Whereas *e.g. Collman*[36] and *West*[37] initially assigned the first band in the carbonyl region at 1578 cm^{-1} empirically to the C=O and the second at 1527 cm^{-1} to the C=C stretching vibration, *Nakamoto*[38] and his coworkers concluded from a normal coordinate analysis that the first band has 75% C=C and only 25% C=O character, while the second band arises from the same bonds with the proportions reversed. *Mecke* and *Funk*[39] avoid attributing these bands to discrete group frequencies, since localization of the vibrational energy in a certain bond cannot be expected if the vibrations are extensively coupled, and they suggest that these four bands should be regarded as characteristic stretching vibrations of the chelate ring as a whole, as in the case of benzene.

Uncertainties in the assignment of frequencies in the vibrational spectrum can be eliminated experimentally if individual atoms in the molecule under study are replaced by heavy isotopes. According to the vibration equation for a harmonic oscillator [eq. (1)], this leads to a displace-

$$\nu = \frac{1}{2\pi}\sqrt{\frac{k}{m}} \qquad (1)$$

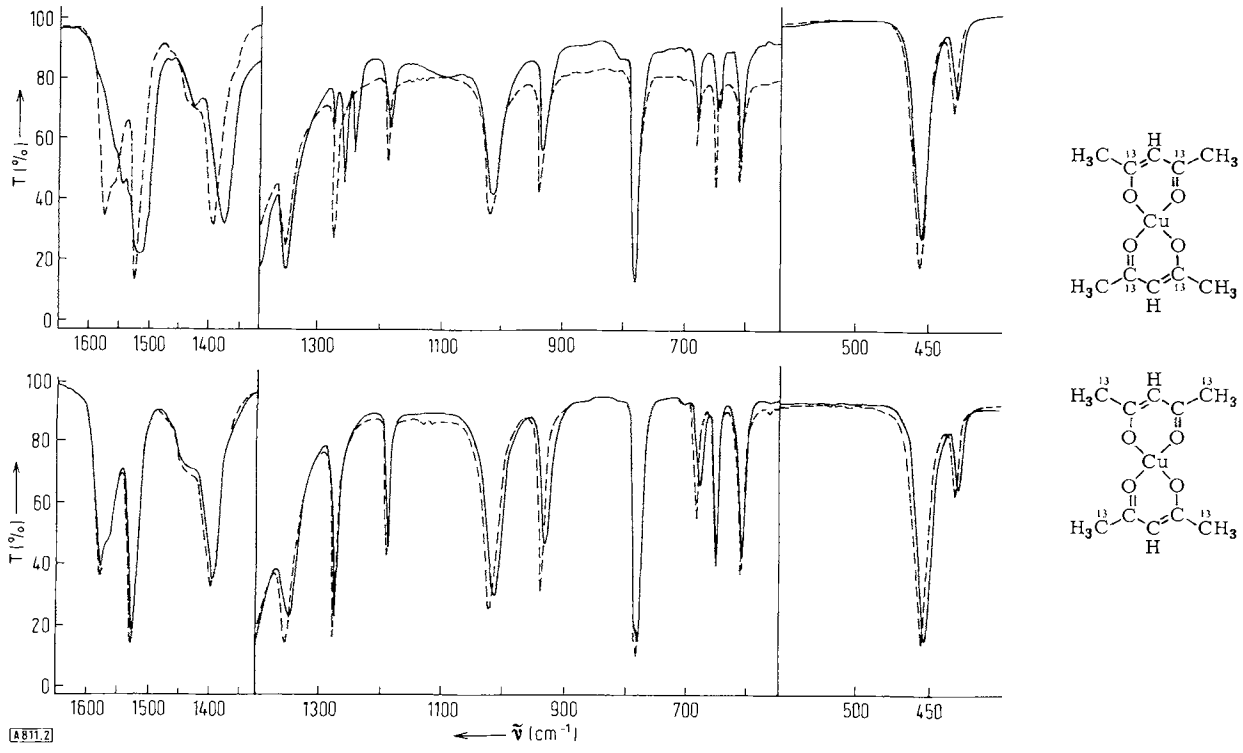


Fig. 2. IR spectrum of the copper bis(2,4-pentanedionate) complex, unlabeled ---, above [2,4-$^{13}C_2$]-labeled, below [1,5-$^{13}C_2$]-labeled.

ment of the absorption band to longer wavelengths, since the mass of the vibrating atoms is in the denominator in the square root. With only 50% labeling of the atoms, two bands appear in the spectrum (Fig. 3), and the difference

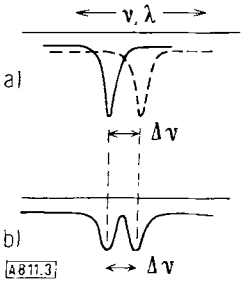


Fig. 3. (a) Frequency shift due to 100% incorporation of a heavy isotope ---; (b) vibrational spectrum of a molecule with 50% labeling with a heavy isotope.

between the vibrations of the unlabeled and of the labeled molecules can be calculated and is a measure of the extent of the movement of the labeled atom in the vibration. It is assumed here that the force constant does not change on isotopic substitution, an assumption that is sufficiently valid even for the greatest possible change, *i.e.* replacement of hydrogen by deuterium[40]. In the spectrum of a compound with many atoms (29 in this case), the equations become correspondingly complicated, and the vibrations are more or less strongly coupled, so that several bands are displaced at the same time[41]; however, one can see directly which frequencies in the spectrum are associated with a given atom[42]. If this atom does not move in a given vibrational mode of the molecule, the band in question will not be affected by isotopic substitution.

Consequently, as many of the atoms of 2,4-pentanedione as possible were replaced both singly and in the combinations shown in Fig. 4, by the isotopes ^{13}C, ^{18}O, and ^{2}H (more than 50% enrichment). The spectra of the complexes with various metals were recorded and numerous band shifts observed. The comprehensive results may be summarized and evaluated in the amplitude diagrams in Fig. 5[43,44].

If the magnitude of the shift of a given band is represented by a circle of corresponding size around the labeled atom in the formula, one can immediately see how strongly each atom participates in the vibration in question. The direction of vibration is deliberately omitted, since it is not immediately evident from the band shift. The band at

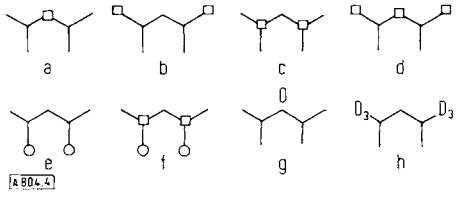


Fig. 4. List of isotopically labeled 2,4-pentanediones (a–h). □, ^{13}C 50% enriched; ○, ^{18}O 70% enriched; D, ^{2}H more than 90% enriched.

1578 cm^{-1} is displaced by −30 cm^{-1} toward longer wavelengths (Figs. 2 and 5) when C atoms 2 and 4 are exchanged for ^{13}C. If the atoms 1, 3, and 5 are substituted by ^{13}C, this band undergoes only an extremely small shift, whereas replacement of the O atoms by ^{18}O leads to a displacement of the same band by −26 cm^{-1} to lower frequencies. This band thus clearly has a high C—O stretching character, whereas the second band at 1527 cm^{-1} is the antisymmetric vibration of the C—C—C segment

of the chelate ring, and the fourth band at 1281 cm^{-1} is the corresponding symmetric vibration, in which C atoms 2 and 4 move in the same direction toward or away from C-3. The third band at 1397 cm^{-1} is again mainly a C—O vibration, and most of the other bands in the spectrum can be assigned in the same way. The bands due to deformational vibrations are located in the center of the spectrum (Fig. 2), and the metal-oxygen frequencies at longer wavelengths[44].

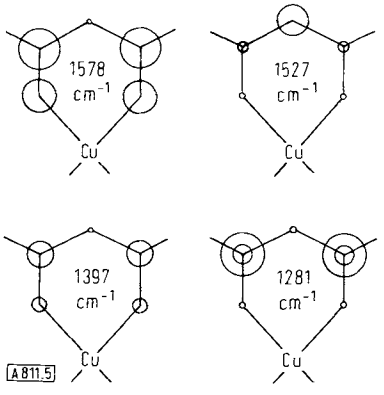


Fig. 5. Amplitude diagrams for some bands from the IR spectrum of copper bis(2,4-pentanedionate). The circles show the magnitude of the long-wave shift of the frequencies in question when these atoms are replaced by heavy isotopes.

The assignment discussed here, particularly of the C—O and C—C—C bands, was also deduced by other workers from ^{18}O-labeling experiments[45]. However, normal coordinate analyses do not lead definitely to the desired information for this molecule containing 29 atoms. More recent calculations for the Cu and Eu complexes[46] give the same result as the earlier calculations[38], but agreement with the experimental assignment given here was achieved by improvement of the force field used for the first calculation[47]. Measurements have recently also been carried out on pentanedionates highly enriched in heavy metal isotopes ($^{54}Fe/^{57}Fe$, $^{50}Cr/^{53}Cr$, $^{63}Cu/^{65}Cu$, $^{104}Pd/^{110}Pd$) to verify the assignment of the metal-oxygen vibrations[48].

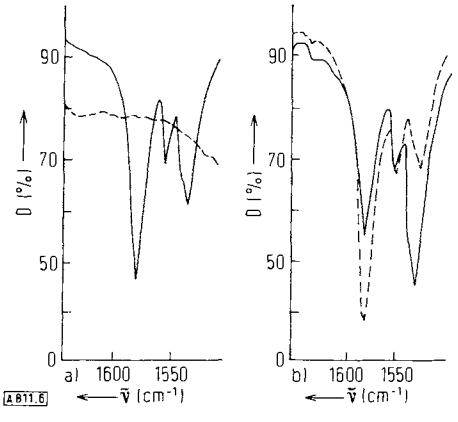


Fig. 6. (a) —— IR spectrum of copper bis(2,4-pentanedionate) in stretched polyethylene film, thickness 4×10^{-3} cm without polarizer against polyethylene film of thickness 4×10^{-3} cm. --- IR spectrum of a stretched polyethylene film of thickness 4×10^{-3} cm against air. (b) IR spectrum of copper bis(2,4-pentanedionate) in drawn polyethylene film of thickness 4×10^{-3} cm against polyethylene film of thickness 4×10^{-3} cm, with polarizer, ⊥ perpendicular —— and ∥ parallel --- to the stretching direction.

The question which of the two C—O vibrations is the antisymmetric and which the symmetric can be answered with the aid of the spectra of molecules oriented in stretched films with polarized IR light. The molecules are oriented with their longitudinal axes in the stretching direction, and the intensity of the bands is high when the plane of polarization of the radiation coincides with the direction of the transition moment of the vibration, and low when the two vectors are perpendicular to each other. It can be seen from Fig. 6 that the band at 1578 cm^{-1} is caused by the symmetric C—O vibration[44]. The organic chemist tends to accept that the antisymmetric vibration *e.g.* for the NH_2, NO_2, and $CO_2^{\ominus}$ groups has the higher frequency, but this is strongly dependent on the angle between the two vibrations.

4. Symmetry of the Chelate Ring

It can be seen that the symmetric stretching vibration of the C—C—C segment at 1281 cm^{-1} in the spectrum of the [2,4-$^{13}C_2$]-labeled Cu complex splits into three equidistant sharp bands with very different intensities, and the shifts are -16.5 and -33.5 cm^{-1}. Since this can provide considerable information about the symmetry of the complex, let us enlarge this pattern of bands in Figure 7 and analyze it in more detail.

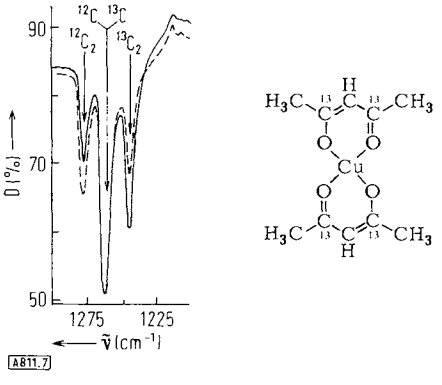


Fig. 7. Splitting pattern of the band at 1281 cm^{-1} for the copper bis(2,4-pentanedionate) complex at various levels of labeling with ^{13}C (——, 52.5% [$^{13}C_1$]acetic acid as starting material; ---43.9%).

The starting material for the synthesis of the complex was acetic acid in which the carboxyl group had been enriched in ^{13}C to 52.5%. The product thus consists of a mixture of 22.6% of unlabeled molecules, 49.9% of molecules containing only one ^{13}C atom in position 2 or 4, and 27.6% of molecules doubly labeled in these positions. Since the intensities of the three bands in the spectrum correspond to these percentages, the first band is assigned to the unlabeled complex, the second to the singly labeled complex, and the third to the doubly labeled complex. That this assignment is correct can be easily shown by starting with an acetic acid sample with 43.9% $^{13}C_1$; in this case the intensities of the three bands change in accordance with the calculated ratio to 31.5, 49.2, and 19.3%.

This band splitting is related to the symmetry of the molecule as follows. In a molecule A in which the bonds between

an atom M2 and two other atoms M1 and M3 of the same kind differ in strength (Fig. 8), replacement of the atom M1 by a heavy isotope will lead to a pronounced displacement of the stretching vibration ν_{M1-M2} (ν_2) and a small shift of the second stretching vibration ν_{M2-M3} (ν_1) because of

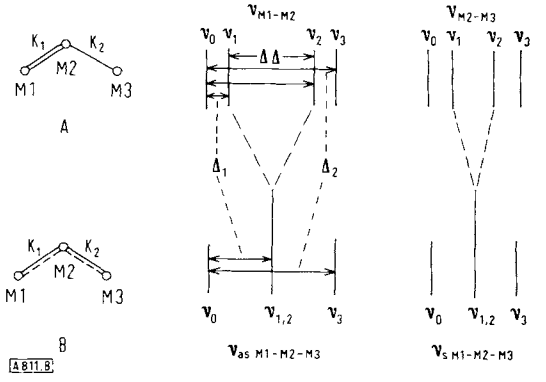


Fig. 8. Splitting of the stretching vibrations for the unsymmetrical case A and the symmetrical case B.

coupling, both displacements being to longer wavelengths. The same is true when atom M3 is labeled. If both M1 and M3 are replaced, both frequencies will exhibit an even greater shift (ν_3). The IR spectrum of a mixture of all three types of labeled molecules must therefore show three displaced partial bands (ν_1, ν_2, and ν_3) for both bands, as well as the component for the unsubstituted molecule ν_0. If the force constants of the two bonds are equal, as in B (Fig. 8, $K_1 = K_2$), the vibrational spectrum will also show two stretching vibrations, *i.e.* one antisymmetric and one symmetric. In contrast with A, the replacement of M1 is no longer distinguishable from that of M3, and the two middle frequencies ν_1 and ν_2 in the splitting pattern for the bands of the mixture coincide. Each band of B gives a triplet, and the ratio of the shifts for the components of each triplet Δ_1 and Δ_2 must be 1:2. If the shifts for an angular C—C—C system in which ^{12}C has been replaced by ^{13}C are calculated by starting with a single and a double bond (A, $K_1/K_2 = 2.0$) and making the force constants

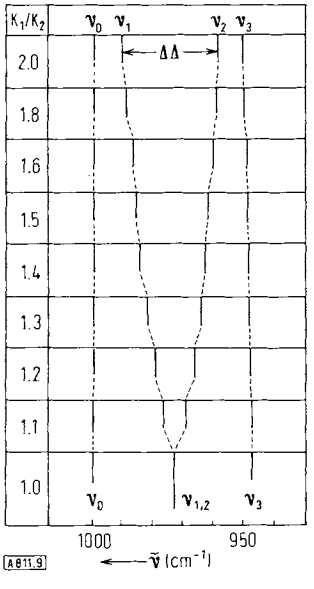


Fig. 9. Calculated splitting for various force constant ratios K_1/K_2.

between the atoms more and more similar until they are exactly equal as in B ($K_1/K_2 = 1.0$), one can see from Fig. 9 that the difference $\Delta\Delta$ between the middle components ν_1 and ν_2 decreases steadily. For a difference of 10% in the force constants ($K_1/K_2 = 1.1$), we obtain a splitting of 3.5 cm^{-1}. The experimental error of ± 1 cm^{-1} in the IR spectrum corresponds to a difference of 3% in the force constants. When converted into bond lengths, this corresponds to an accuracy of ± 0.01 Å for the difference or identity of the bond lengths, which is as good as, and in many cases better than, that of a careful X-ray analysis.

The IR spectrum of partly labeled products thus offers the possibility of a definite answer as to whether there is an equilibrium between tautomeric or valence-isomeric structures or only one structure with complete delocalization of single and double bonds (double or single minimum in the energy profile, Figs. 1 and 8). However, two important conditions must be satisfied. It must be possible to locate the corresponding bands with certainty in the spectrum, and the half-widths of the bands in the splitting pattern must be small in relation to their shift with respect to the unlabeled compound.

Table 1. Shift of the 1281 cm^{-1} band of copper bis(2,4-pentanedionate) on substitution of C atoms 2 and 4 with ^{13}C.

	Δ1	Δ2
Calculated:	17.2 cm^{-1}	33.3 cm^{-1}
Experimental:	16.5 ± 1 cm^{-1}	33.5 ± 1 cm^{-1}

These conditions are satisfied by many metal complexes of acetylacetone. The half-widths of the three partial bands (Fig. 7) in the spectra of the complexes with Cu, Li, Na, Mg, Be, and Pd agree to within ± 1 cm^{-1} both in the crystal and in solution. Thus the force constants between the C atoms of the chelate ring are equal, and the delocalization of the double bonds is complete[49, 50]. The observed

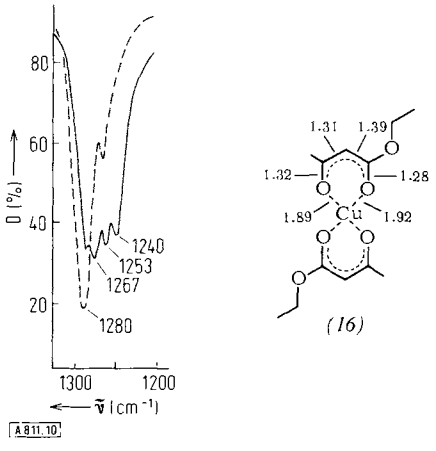


Fig. 10. Section of the IR spectrum of the [1,3-$^{13}C_2$]-labeled Cu complex of acetoacetic ester *(16)*; unlabeled ---.

shift of the band at 1281 cm^{-1} agrees with the value calculated for the symmetrical molecule *(7)* (Table 1)[51] within experimental error.

In order to check this conclusion measurements were also carried out on the copper complex of [1,3-$^{13}C_2$]-labeled acetoacetic ester. According to X-ray analysis *(16)* the C—C distances in the ring are significantly different, and have values of 1.31 and 1.39 Å (±0.025)[52], corresponding to a force constant ratio of 1.3.

The spectrum (Fig. 10) does in fact show three displaced bands, and the shift difference $\Delta\Delta = 14\ cm^{-1}$ corresponds to a force constant ratio of 1.4 or a difference of 0.1 Å in the bond lengths[50].

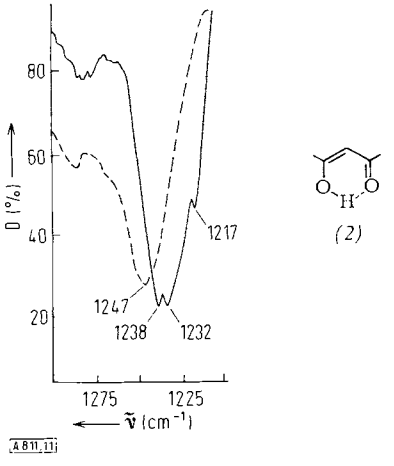
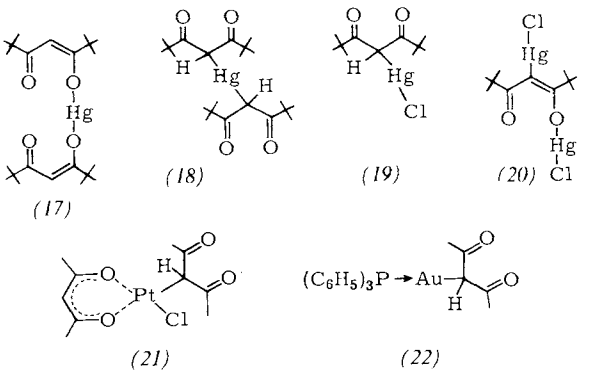


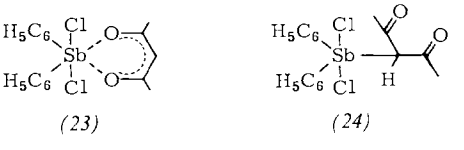
Fig. 11. Section of the IR spectrum of [2,4-$^{13}C_2$]-labeled pentanedione *(2)*; unlabeled---

In the case of [2,4-$^{13}C_2$]-pentanedione, the IR spectrum at room temperature shows only one C—C—C band of the enol form at about 1240 cm^{-1}, with pronounced broadening toward longer wavelengths. For the crystalline enol, at −176 °C, the band is so much sharper that the splitting of the middle components ν_1 and ν_2 (6 cm^{-1}) becomes clearly recognizable (Fig. 11)[50]. The ratio of the force constants is thus 1.20. A normal coordinate analysis of the entire spectrum carried out by *Nakamoto*[53] gave $K_1/K_2 = 1.18$.

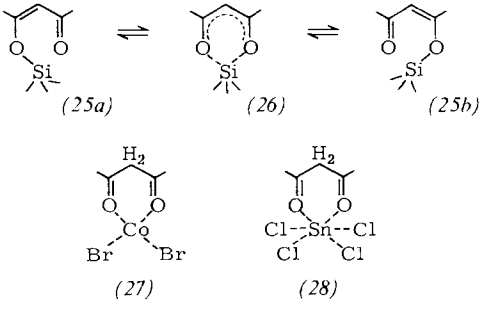
5. C-Bonded Heavy Metal Complexes of 2,4-Pentanedione

The IR spectra of very many metal complexes of 2,4-pentanedione all indicate the same type of bonding in the region between 1500 and 1600 cm^{-1}[54]. Force constants are given for the metal-oxygen bond[46], and the π-bonding mechanism is discussed[55]. A marked exception is mercury, which tends to arrange organic ligands in a linear manner[56], and whose very sparingly soluble complex with 2,4-pentanedione gives a sharp and intense C=O band at 1678 cm^{-1} in the IR spectrum. *Nonhebel*[57] has proposed the open enolate structure *(17)* for the more soluble complex of mercury with 2,2,6,6-tetramethyl-3,5-heptanedione which gives the same IR band. However, the NMR spectrum of this compound at −40 °C in $CDCl_3$ indicates an H—C—^{199}Hg coupling of $J = 221$ Hz in the signal for the proton on the central C atom at −4.86 ppm[58]. β-Diketone residues must therefore be bonded to the mercury by the C-3 atoms, as shown in *(18)*. The NMR spectrum also shows about 3% of enolate structures [*e.g. (17)*]. To rule out mercury salt catalyzed ligand exchange[31] during the NMR measurement, the β-diketones were treated with bis(hexamethyldisilylamido)mercury[60] according to the method used by *Lorberth*[59] for the preparation of pure dicyclopentadienylmercury *(13)*; the mercury compound formed from pentanedione in this way was obtained in an analytically pure state for the first time. All earlier methods give products that contain larger or smaller amounts of OH, acetate, or chloride[61,62]. C-Bonded structures have also been deduced for the mercury halide complexes from the IR spectra [*(19)*, C=O 1684 cm^{-1}; *(20)*, C=O 1668, C=C 1602 cm^{-1}][61-63]. According to IR[64], NMR[65], and X-ray analyses[66] in ionic platinum chloride complexes, one pentanedione is in the form of a chelate and the other is C-bonded *(21)*, as is also reported for the gold complex *(22)*[67]. In the dichlorodiphenylantimony complex, the equilibrium between the chelate *(23)* and the C—Sb form *(24)* is established so slowly that both forms can be recognized in the NMR spectrum[68].





It is well known that boron is incorporated into the chelate ring as RB or F_2B[69-71]. Trialkylsilyl enol ethers of β-diketones form *cis-trans* isomers. A chelated transition state *(26)* with an activation energy of 13.8 kcal/mole is reported[72] for the fast equilibration of the trimethylsilyl group between the O atoms of the *cis* form *(25)*. Complexes of pentanedione with cobalt and bromine[73], tin, titanium, and zirconium tetrachlorides[74], and nickel[75]



have also been described, to which, on the basis of the IR spectra (bands 1700–1722 cm^{-1}), structures [*e.g. (27)* and *(28)*] are assigned in which the keto form is coordinated *via* the two oxygen atoms; some of these can be readily converted into chelates.

6. Magnetic Anisotropy of the Chelate Rings

It can be seen from the foregoing discussion that a chelate, an open enolate, and a C-bonded structure can be distinguished easily and with certainty on the basis of the vibrational spectrum. Complete equalization of the bonds and the symmetry of the ligands can also be established by an accurate analysis of the spectra of partly labeled products. It is asking too much of vibrational spectroscopy, however, to use it in attempts to compare the bonding in the chelate ring with that in benzene, even though the metal-oxygen bond should have some π character.

The effect of the magnetic anisotropy of an aromatic ring on the position of a proton signal in the NMR spectrum is well known[76, 77] (Fig. 12), and is nowadays accepted as perhaps the simplest experimental criterion of aromatic

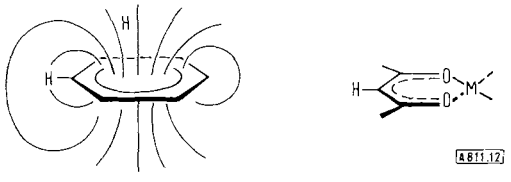
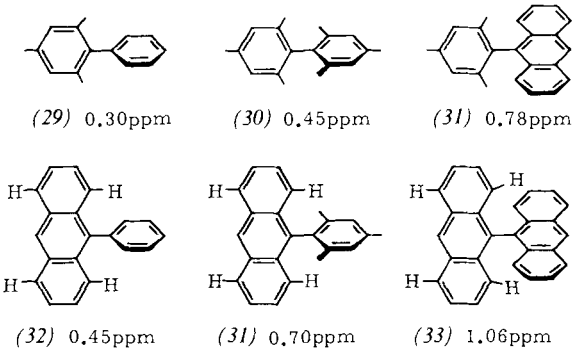


Fig. 12. Comparison of the magnetic anisotropy of the benzene and chelate rings.

character. Protons in the plane of the aromatic ring are shifted downfield, and protons above and below this plane to higher fields, and the magnitude of the shift can be calculated[77]. Impressive examples of the application of this concept are *ansa* compounds[78], cyclophanes[79], annulenes[80], bridged annulenes[81], *trans*-15,16-dimethyldihydropyrene[82], and polycondensed systems of the azulene type[83].

Numerous attempts to deduce the aromatic character of the metal chelates of 2,4-pentanedione from the chemical shift of the signal due to the proton bonded to the chelate ring in the plane of the ring were at first interpreted in very different ways[84]. Some authors argued in favor of aromaticity[85, 86], while others argued increasingly against it[70, 87, 88]. The position of these protons is evidently influenced by polar effects[89], and this is supported by calculations on the shift of the C—H signals and of the ^{13}C—H coupling with the aid of the electric field in the plane of the ring[90, 91].

To establish in some other manner whether or not cyclic conjugation of 6 electrons *via* the metal atom really does occur in these chelates and whether it produces a magnetic anisotropy effect comparable to that observed with benzene, pentanedionates were prepared in which protons are situated above and below the plane of the chelate ring[92, 93]. The NMR spectra of the model compounds *(29)* to *(33)* show the magnitude of the shifts to be expected for such protons in aromatic systems. The difference $\Delta\delta$ in the shifts of the *o*- and *p*-methyl groups in the NMR spectra of phenylmesitylene *(29)*, bimesityl *(30)*, and 9-mesitylanthracene *(31)* and of the 1,8- and 4,5-H atoms in 9-phenylanthracene *(32)*, *(31)*, and 9,9′-bianthryl *(33)* show that a difference of about 0.5 ppm should be observed if the system is truly aromatic. The differences in the case of the models (0.30–1.06 ppm) are due partly to the somewhat different average twisting angles of the two aromatic systems in relation to each other, and partly to the fact that the 1,8-anthryl hydrogen atoms are more firmly fixed



above the other ring than the hydrogen atoms of the rapidly rotating methyl groups, for which only average values are recorded for favorable and unfavorable positions with respect to the other ring. Finally, the electron densities in the phenyl, mesityl, and anthracene rings are naturally different. It should be mentioned that calculation of these shifts by the usual methods[77] leads to values that agree satisfactorily with the experimental values, even if the local contributions of the atoms to the total anisotropy are taken into account[94] [*e.g.* calc. 0.50 for *(30)*, 0.80 for *(30)*].

The NMR spectra of the corresponding mesityl- and anthryl-substituted acetylacetones [*(34)* and *(35)*] and their metal chelates give shift differences of 0.20 and 0.05 ppm, respectively, that deviate only very slightly within the limits of error ($\pm$0.02 ppm), regardless of whether the measurements are carried out on the free acids, the alkali metal salts with K, Na, and Li, which are more or less dissociated in dimethyl sulfoxide, or the chelates with Be, Al, Co, and Pd (Table 2). With increasing stability of the

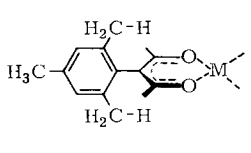
Table 2. $\Delta\delta$ values from the NMR spectra of *(34)* and *(35)*.

	(34)			*(35)*	
M	Solvent	$\Delta\delta$	M	Solvent	$\Delta\delta$
H	$CDCl_3$	0.20	H	$CDCl_3$	0.05
H	DMSO	0.19	H	DMSO	0.10
K	DMSO	0.17	K	DMSO	0.13
Na	DMSO	0.13	Li	DMSO	0.07
Li	DMSO	0.14	Be	$CDCl_3$	0.12
Be	$CDCl_3$	0.14	Pd	$CDCl_3$	0.08
Al	$CDCl_3$	0.13			
Co	$CDCl_3$	0.16			
Pd	$CDCl_3$	0.22			

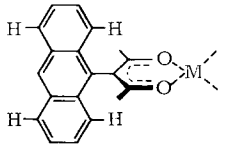
complex, there is no additional shift of the protons above the plane to higher magnetic fields, and the values for the anthryl derivatives *(35)* are smaller instead of greater than those for the mesityl compounds *(34)*. Thus at least the angular C—C—C part of these chelate rings has no mag-

netic anisotropy comparable with that of benzene, and if this is accepted as a criterion no argument can be deduced favoring aromatic bonding in the β-diketone metal chelates examined here[92].

Further chelates with other metals will naturally also have to be examined, and it would be interesting to use aromatic models in which the electron density in the ring is systematically varied by means of suitable substituents and in which the rings carry, *e.g.* positive and negative charges. It should also be pointed out that there is room for improvement in the accuracy of the Δδ values. The analysis of the spectra of the anthryl derivatives [*(31)–(33)* and *(35)*] is that of a frequently not very well resolved ABCDX spectrum[95]. The 2,3,6,7-tetramethylanthryl derivatives were prepared in some cases to facilitate the determination of Δδ from the spectrum[93].



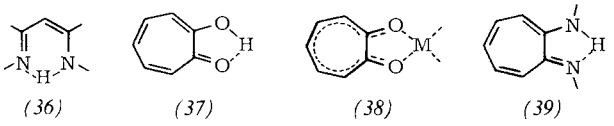
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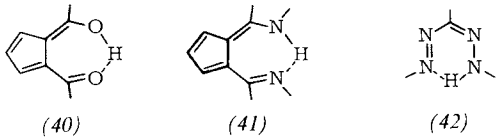
(35)

This result is contradicted by more recent studies, in which it is deduced from the electronic spectra and from NMR and ESR data for some heavy metal chelates of β-diketones that donor or acceptor π bonds of various strengths occur between the metal and the oxygen, depending on the metal[96, 97]. However, if one attempts to drive an electron around the chelate ring in accordance with the ring current model[77] it has to overcome a relatively high potential barrier at the metal atoms and falls into a relatively deep potential well at the oxygen, whereas this does not occur in a similar treatment for benzene[98, 99].

Daltrozzo[100, 101] independently reaches the same conclusion regarding the bonding in β-diketone chelate rings by analysis of the intensities in the fine structure of electronic spectra and from NMR spectra. According to this author, the amino-imino derivatives of β-diketones *(36)*, just like the enol form of 2,4-pentanedione *(2a)*⇌*(2b)*, are not symmetrical[102].



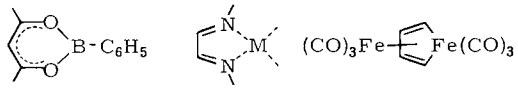
(36) *(37)* *(38)* *(39)*



(40) *(41)* *(42)*

The same is true of tropolone *(37)*[103] and its amino-imino derivative *(39)*[104] and of the compounds *(40)*[105], *(41)*[106], *(42)*[107] for which symmetrical structures similar to *(3)* and the term "nonclassical aromatic systems" had formerly been proposed[104, 108, 109]. The bond delocalization is probably again complete in the anions and metal chelates, as is indicated by the X-ray analyses of the tropolonates *(38)*[110].

It now seems interesting to use the method described here to examine many other ring systems to which a more or less aromatic character has been attributed on the basis of



(43) *(44)* *(45)*



(46) *(47)*

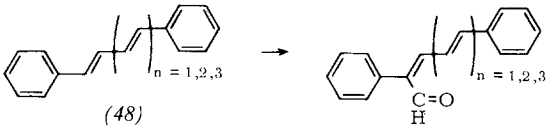
the chemical shift of their protons in the plane of the ring or other criteria; examples of such systems are phenylboron chelates *(43)*[69, 70], metal complexes of glyoxal diimine *(44)*, butadienyliron carbonyls *(45)*[111], and many nitrogen, sulfur, and oxygen heterocycles, *e.g. (46)* and *(47)*[112].

7. Conclusion

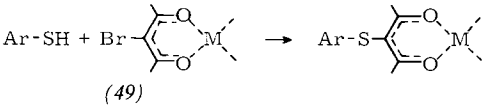
Formerly, the only way in which a chemist could determine the character of a bond was by comparison of chemical reactions in which the bond, or else a bond in its immediate vicinity is broken or formed. The arguments involved were qualitative and frequently very approximate. Chemists have learned how to use quantitative physicochemical measurements for this purpose, such as interatomic distances from X-ray data, force constants from vibrational spectra, and differences in chemical shifts from NMR spectroscopy.

In comparing chelate rings with benzene on the basis of chemical reactivity, one should determine accurate kinetic parameters, and should above all be certain that the reaction used for comparison proceeds by exactly the same mechanism in both cases. This latter condition has not been verified in any case for the reactions mentioned earlier. Moreover, *e.g.* the Vilsmeier formylation also takes place in open-chain systems such as *(48)*[113], and a nucleophilic substitution that does not occur with benzene has recently been observed for the chelate ring *(49)*[114].

One could argue about what is aromatic and whether it is meaningful to look for such a character or for aromaticity in a compound. As long as this concept leads to new compounds and new information about properties, it may be regarded as useful. However, one thing that must be appre-



(48)



(49)

ciated is that the perfection of benzene is lost when any change is made to the molecule. Irrespective of the method of comparison used, benzene is always situated at one end of the scale, and an open-chain or partly hydrogenated system, which is defined as nonaromatic (Fig. 13), at the

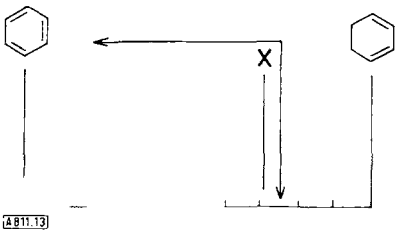


Fig. 13. Gradation of aromaticity from benzene to cyclohexadiene.

other. Anyone can then draw the line in the scale in such a way that his compound X under examination is on the left of the line, and so still appears to be aromatic.

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The Synthesis of Antibiotic Sugars[**]

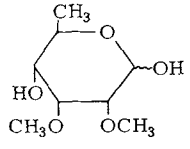
J.S. Brimacombe[*]

The term antibiotic sugar denotes the carbohydrate component of an antibiotic. Two alternative approaches are adopted for the synthesis of these neutral and amino sugars, many of which have unusual structures: One route starts from fairly simple non-carbohydrate precursors, the other depending upon the modification of a carbohydrate precursor.

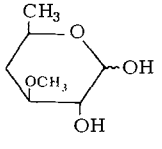
1. Introduction

The term "antibiotic" was introduced[1] into the literature in 1942, although it had been realized for many years that certain microorganisms were able to exert antagonistic effects upon other organisms. In many cases, the antagonist was shown to produce an active, isolable substance (*i.e.*, the antibiotic) which was responsible for the biological activity. Early antibiotics such as gramicidin were effective[2] against pneumococcal and streptococcal infections in animals, and the first clinical use of an antibiotic (streptomycin[3]) was reported in 1944, although *Fleming*[4] had already suggested that penicillin could be used as a dressing for septic wounds.

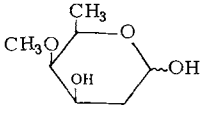
The remarkably successful clinical application of antibiotics in the ensuing years has naturally aroused widespread interest in the organic compounds responsible for the biological activity, and has ensured the intensive investigation of antibiotic substances by structural organic chemists. It has been a particularly active period for carbohydrate chemists since many antibiotics contain sugars of unusual, and often unique, structures[5,6]. Some representative examples are found in the formulas *(1)* to *(18)*; it is notable that a large number of antibiotic sugars possess a 6-deoxy function.



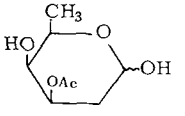
(1) Mycinose



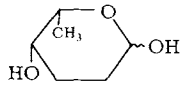
(2) Chalcose



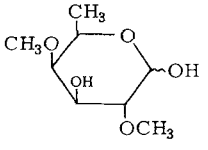
(3) Chromose A



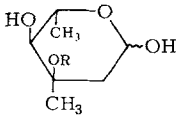
(4) Chromose D



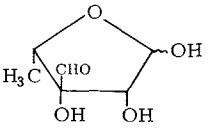
(5) Rhodinose



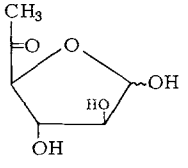
(6) Labilose



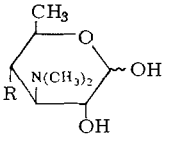
(7), R = H, Mycarose
(8), R = CH_3, Cladinose



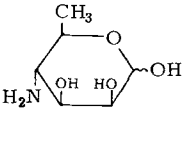
(9) Streptose



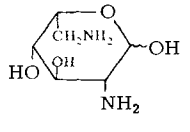
(10) 6-Deoxy-D-arabino-hexofuranos-5-ulose



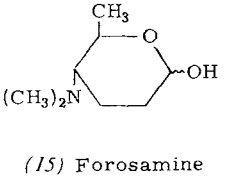
(11), R = OH, Mycaminose
(12), R = H, Desosamine



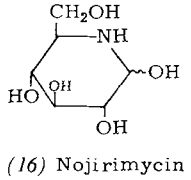
(13) Perosamine



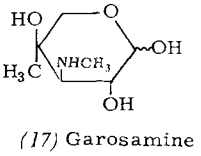
(14) Paromose



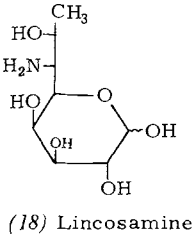
(15) Forosamine



(16) Nojirimycin



(17) Garosamine



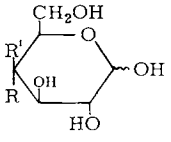
(18) Lincosamine

[*] Prof. J.S. Brimacombe
Department of Chemistry, Dundee University
Dundee, DD1 4HN (Scotland)

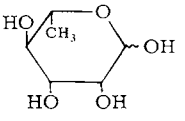
[**] The following abbreviations have been used in the present article: Ac = acetyl; Bz = benzoyl; DCCD = dicyclohexylcarbodiimide; DMF = dimethylformamide; DMSO = dimethyl sulfoxide; Ms = methanesulfonyl; NSB = *N*-bromosuccinimide; Ph = phenyl; Tos = *p*-toluenesulfonyl; Tr = triphenylmethyl (trityl).

There are two approaches that can be applied to the synthesis of these rare antibiotic sugars. One of them uses fairly simple non-carbohydrate precursors as starting materials, whereas the other depends on effecting transformations on carbohydrate precursors. The first approach will lead, of course, to a racemic product which must be resolved if the natural enantiomer is to be obtained. The second method has certainly been more popular, although this may merely reflect the carbohydrate chemist's preference to operate with familiar molecules. Examples of both approaches will be given.

The common sugars carry the highest density of functional groups of any natural product so that transformations on carbohydrate precursors can present some quite intriguing problems. The magnitude of the task can be visualized by comparing the formulas *(1)* to *(18)* with those of the more abundantly occurring sugars such as D-glucose *(19)*, D-galactose *(20)*, and L-rhamnose *(21)*. The validity of this comparison lies in the fact that most syntheses of antibiotic sugars commence from such readily available precursors.



(19), R = OH, R' = H; D-Glucose
(20), R = H, R' = OH; D-Galactose



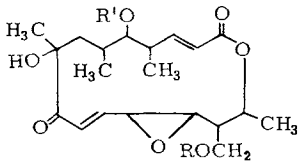
(21) L-Rhamnose

The following examples are fairly representative and were chosen to demonstrate the many diverse synthetic approaches that have been used; in many cases, other equally attractive and definitive syntheses are available.

2. Neutral Antibiotic Sugars

2.1. Mycinose *(1)*

The macrolide antibiotic chalcomycin *(22)* contains two neutral sugars, mycinose[7] and chalcose[8]. Chemical and spectroscopic evidence had identified mycinose as 6-deoxy-2,3-di-*O*-methyl-D-allose *(1)*, an assignment that was verified by a synthesis[9] from 2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-rhamnofuranose *(23)* (Scheme 1).

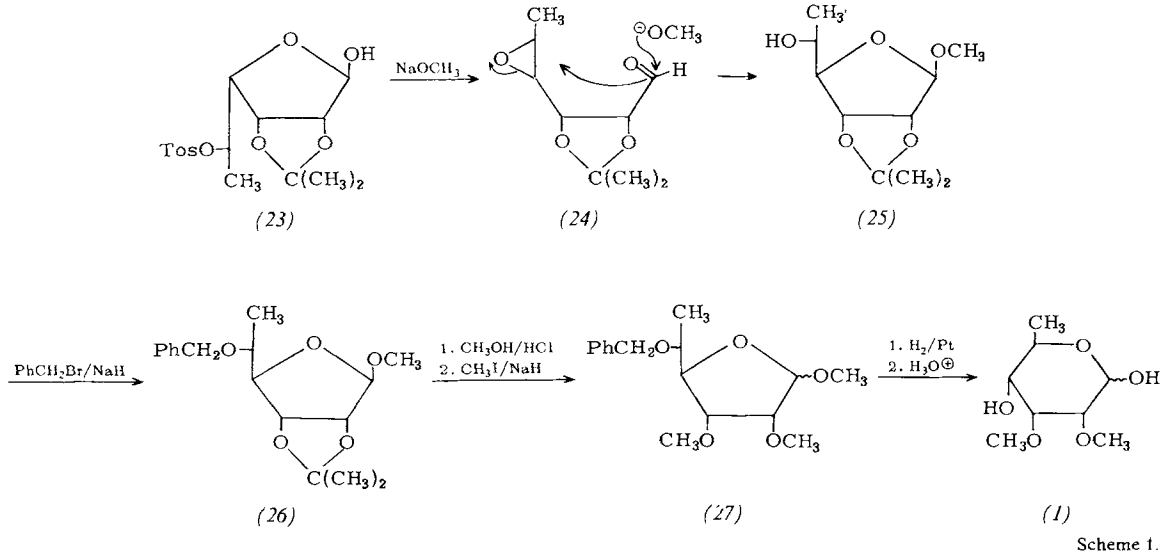


(22)

R = β-Mycinosyl
R' = β-Chalcosyl

Solvolysis of the sulfonate *(23)* with methanolic sodium methoxide converted it into methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside[10] *(25)* by a reaction that involves[11] neighboring aldehyde-group participation in the opening of the intermediate epoxide *(24)*. The overall reaction results in inversion of configuration at both C-4 and C-5 of the initial L-rhamnose derivative, thus providing a ready means of entering the 6-deoxy-D-allose series. Benzylation of *(25)* gave *(26)*, which on sequential methanolysis and methylation yielded methyl 5-*O*-benzyl-6-deoxy-2,3-di-*O*-methyl-D-allofuranoside *(27)*. Catalytic debenzylation of *(27)* followed by acid hydrolysis liberated mycinose *(1)*.

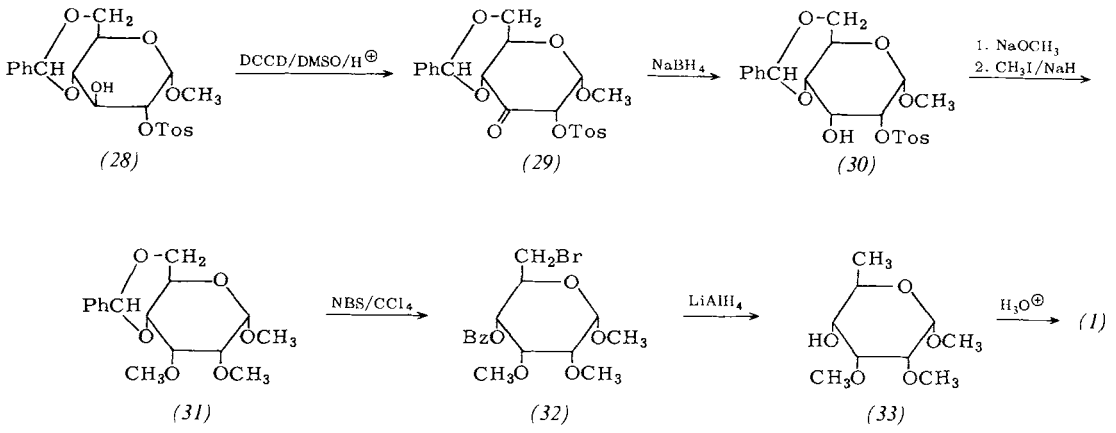
An alternative synthesis of mycinose is available[12] (Scheme 2) whereby entry into the D-allose series was gained by inverting the configuration at C-3 of the D-glucose derivative *(28)* by an oxidation-reduction sequence [*i.e.*, *(28)* → *(29)* → *(30)*]. The oxidation of partially protected sugars has proved troublesome in the past but can now be accomplished[13] efficiently with such oxidants as ruthenium tetroxide[14], the Pfitzner-Moffatt reagent[15] (see Section 2.5), and acid anhydrides in dimethyl sulfoxide[16]. Desulfonylation of *(30)*, with methylation of the resulting diol, gave compound *(31)*. Conversion into the 6-deoxyalloside *(33)* was achieved by the action of *N*-bromosuccinimide in hot carbon tetrachloride on *(31)*, and reduction of the 6-bromo-5-benzoate *(32)* so formed with lithium tetrahydridoaluminate[17]. This procedure provides a very neat way of introducing a 6-deoxy substituent, and is more direct than previous methods which rely on the



(23) *(24)* *(25)*

(26) *(27)* *(1)*

Scheme 1.



Scheme 2.

formation and subsequent displacement of a primary sulfonic ester group. Finally, acid hydrolysis of *(33)* afforded mycinose *(1)*.

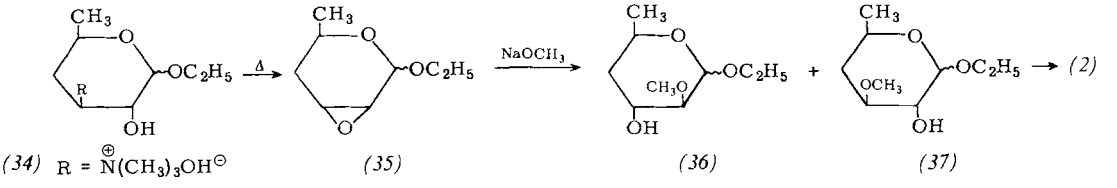
2.2. Chalcose (Lankavose) *(2)*

The structure of chalcose, a component of such antibiotics as chalcomycin *(22)*[18], lankamycin, and neutramycin, was deduced by *Woo et al.*[8,19] to be 4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose *(2)*. Evidence corroborating this structure was provided when it was shown[20] that chalcose could be configurationally related to desosamine *(12)*, an antibiotic sugar of known structure (see Section 3.1).

(Scheme 3) is particularly notable since it demonstrates an elegant way of introducing the deoxy functions.

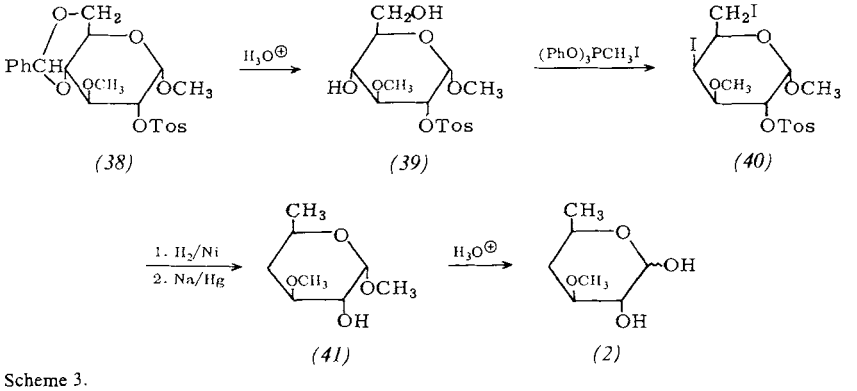
Methyl 4,6-*O*-benzylidene-3-*O*-methyl-2-*O*-*p*-toluenesulfonyl-α-D-glucopyranoside[23] *(38)* was partially hydrolyzed to the diol *(39)*, which was treated with methyl triphenylphosphonium iodide to give methyl 4,6-dideoxy-4,6-diiodo-3-*O*-methyl-2-*O*-*p*-toluenesulfonyl-α-D-galactopyranoside *(40)*. Hydrogenolysis of *(40)* followed by cleavage of the sulfonate group with sodium amalgam yielded the 4,6-dideoxyglycoside *(41)*, which was hydrolyzed with acid to chalcose *(2)*.

Racemic chalcose has been prepared[24] from non-carbohydrate precursors by the route outlined in Scheme 4. The key intermediate *(43)* for the synthesis was prepared[25]

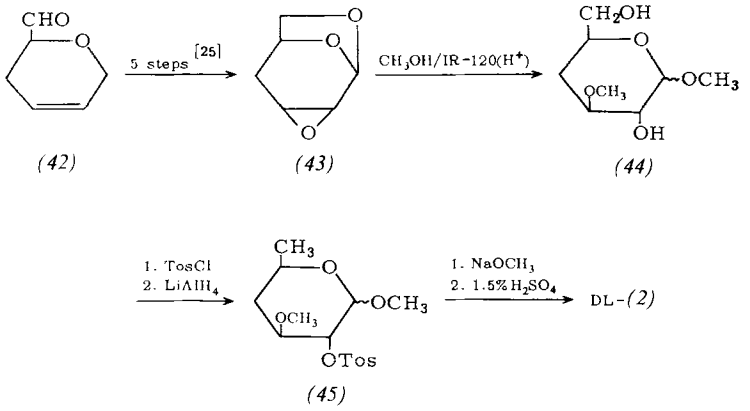


This was achieved by pyrolysis of the desosaminide derivative *(34)* to give the epoxide *(35)*, which afforded a mixture of isomeric methyl ethers *(36)* and *(37)* on ring-opening with boiling sodium methoxide. Acid hydrolysis of one of these isomers *(37)* gave chalcose.

Several stereospecific syntheses of chalcose have been reported[21], but that developed by *Kochetkov* and *Usov*[22] from acrolein dimer *(42)*, and it underwent acid-catalyzed opening of the epoxide ring in boiling methanol to give a mixture of the anomeric methyl 4-deoxy-3-*O*-methyl-DL-*xylo*-hexopyranosides *(44)*. Thereafter, the 6-deoxy function was introduced using a conventional displacement of the 6-*p*-toluenesulfonate with lithium tetrahydridoaluminate. Successive treatments of the resulting 4,6-dideoxy derivative *(45)* with sodium methoxide and dilute sulfuric



Scheme 3.



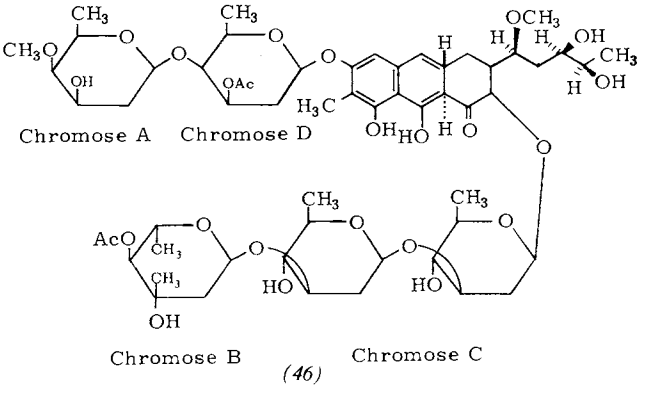
Scheme 4. IR-120(H^+) is an ion exchanger in acidic form.

acid produced DL-chalcose, but resolution of the racemate was not attempted.

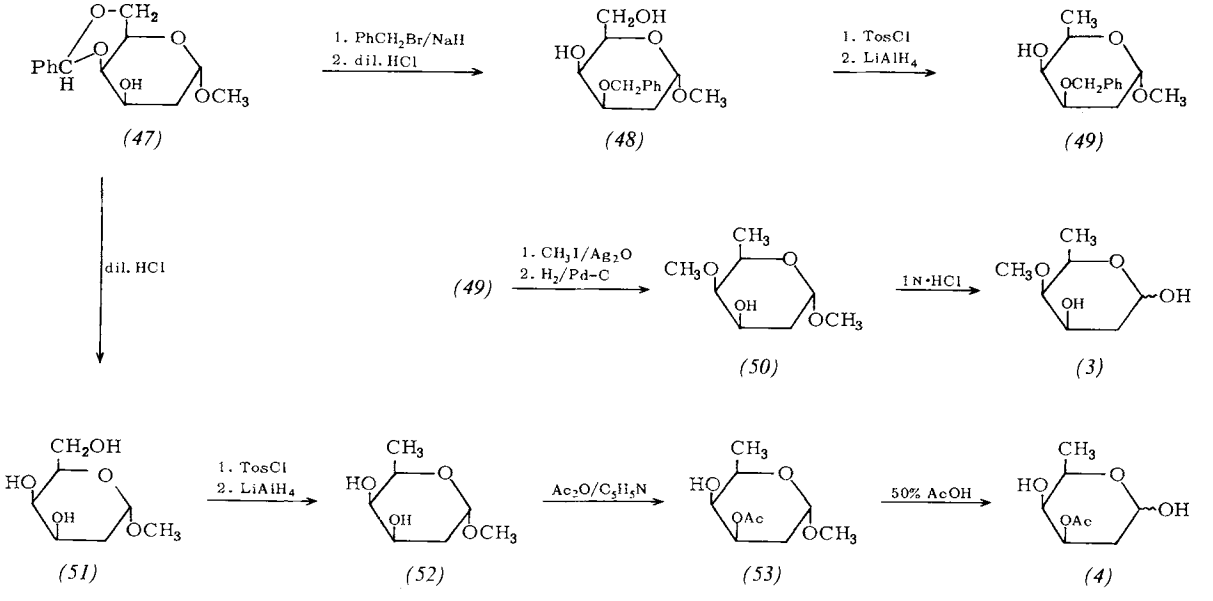
2.3. The Chromoses

Chromomycin A_3 is the principal constituent of a group of cancerostatic and antitumor antibiotics produced[26] by *Streptomyces griseus* No. 7; closely related antibiotics are aureolic acid, olivomycin, aburamycin, and mithramycin. The structure of chromomycin A_3 is probably that shown in formula *(46)*, although the configurations of the glycosidic linkages have not been settled beyond dispute. The four sugar components of chromomycin A_3 are[27] 2,6-dideoxy-4-*O*-methyl-D-*lyxo*-hexose [*(3)*, chromose A], 4-*O*-acetyl-2,6-dideoxy-3-*C*-methyl-L-*arabino*-hexose (chromose B), 2,6-dideoxy-D-*arabino*-hexose (chromose C or olivose), and 3-*O*-acetyl-2,6-dideoxy-D-*lyxo*-hexose [*(4)*, chromose D]; a fifth 2,6-dideoxyhexose having the structure 2,6-dideoxy-4-*O*-isobutyryl-3-*C*-methyl-L-*arabino*-hexose (chromose B') is encountered[26] in chromomycin A_2.

The assignments of structure to chromoses B and C were decided[27] on the basis of spectroscopic evidence and from comparisons with known compounds. The structure of chromose A *(3)* was confirmed[28] by a synthesis from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside *(47)*. The route used (Scheme 5) requires little detailed comment since, once the C-3 hydroxyl group had been protected by benzylation, the functionalities at positions 4 and 6 were introduced by straightforward reactions.



The synthesis of chromose D *(4)* posed a more interesting problem since it required the selective acylation of a *cis*-diol system. Unimolecular acetylation of the 6-deoxyglycoside *(52)* gave[29] mainly the required 3-acetate *(53)*, the product predicted on conformational grounds; this assignment was reinforced by an unequivocal synthesis[29] of the isomeric 4-acetate. Partial hydrolysis of *(53)* with hot 50% acetic acid liberated the free sugar *(4)*, which proved to be identical with chromose D. Deacetylchromose D has been discovered[30] recently in chromocyclomycin, a new streptomycete metabolite possessing antitumor activity.

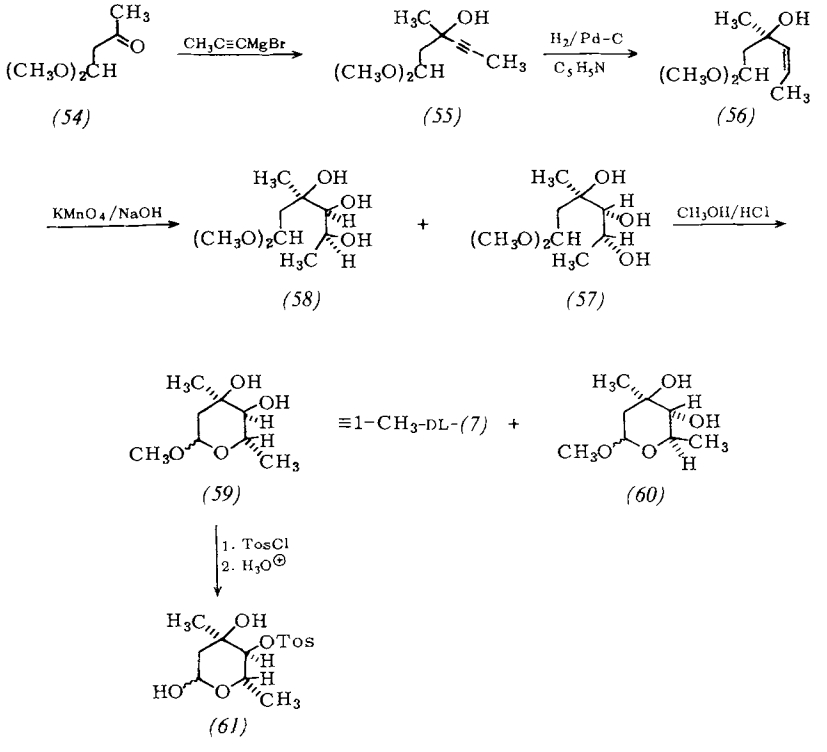


Scheme 5.

2.4. Mycarose *(7)* and Cladinose *(8)*

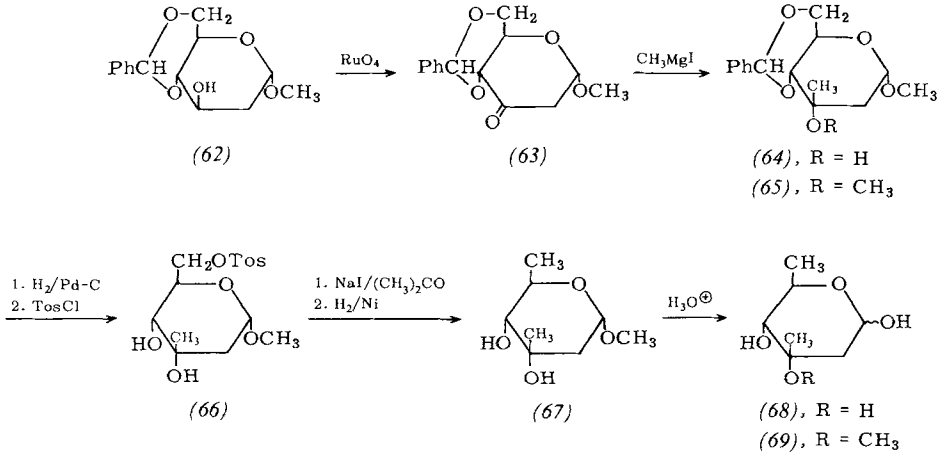
The structure of mycarose, a component of antibiotics such as magnamycin, spiramycin, and tylosin, is now firmly established[31] as 2,6-dideoxy-3-*C*-methyl-L-*ribo*-hexose *(7)*. The antibiotic sugar cladinose *(8)* (from erythromycin) is the 3-methyl ether of mycarose, and is converted into mycarose on demethylation with boron trichloride[32].

Preliminary investigation indicated[33] that mycarose was a branched-chain sugar which could be generally formulated as a 2,6-dideoxy-3-*C*-methylaldohexose. As there was no clear evidence for the relative configuration at the three asymmetric centers, *Woodward et al.*[34] devised a scheme which would lead to the four possible racemates; the reactions which eventually established the stereochemistry of mycarose are shown in Scheme 6. In brief, the acetal *(54)* was condensed with 1-propynylmagnesium bromide to give the acetylenic alcohol *(55)*, which was converted into the *cis*-alkene *(56)* following partial hydrogenation over a poisoned palladium catalyst. *cis*-Hydroxylation of *(56)* and cyclization of the resulting triols *(57)* and *(58)* gave a mixture of the racemic glycosides *(59)* and *(60)*. The relative configurations of the separated glycosides were elucidated by chemical means, and the relationship of racemic *(59)* to mycarose was demonstrated by its conversion into the *p*-toluenesulfonate *(61)*, which was spectroscopically indistinguishable from the corresponding natural sugar derivative.



(54) *(55)* *(56)* *(58)* *(57)* *(59)* *(60)* *(61)*

Scheme 6.



(62) *(63)* *(64)*, R = H *(65)*, R = CH_3 *(66)* *(67)* *(68)*, R = H *(69)*, R = CH_3

Scheme 7

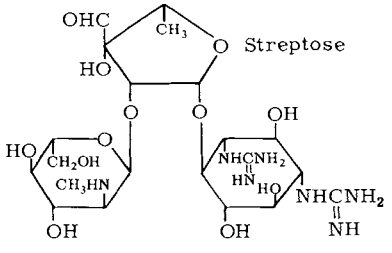
Racemic *(59)* was resolved by means of the hydroxybornane sulfonic esters and, finally, the absolute configuration of mycarose was determined[34] by correlating the stereochemistry at C-5 with that of L-lactic acid.

The D-forms of both mycarose and cladinose have been synthesized[35] (Scheme 7) by way of a Grignard reaction on methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose *(63)*, prepared by oxidation of the 2-deoxyglycoside *(62)* with either chromium trioxide or ruthenium tetroxide. A crystalline branched-chain derivative isolated from the reaction was concluded to have the D-*ribo* configuration *(64)* from the existence of intramolecular hydrogen-bonding between the C-1 and C-3 substituents in dilute solutions of carbon tetrachloride; this evidence precluded the alternative D-*arabino* configuration. After catalytic debenzylidenation of *(64)*, the 6-deoxy function was introduced by means of an iodide displacement on the 6-sulfonate *(66)*, whereafter acid hydrolysis of the glycoside *(67)* liberated D-mycarose *(68)*.

An analogous sequence of reactions performed on the methylated derivative *(65)* led ultimately to the synthesis[35] of D-cladinose *(69)*.

2.5. Streptose *(9)*

The component fragments of the antibacterial antibiotic streptomycin *(70)* are streptidine, 2-deoxy-2-methylamino-L-glucose, and the branched-chain sugar streptose[36].



2-Deoxy-2-methylamino-L-glucose Streptidine

(70)

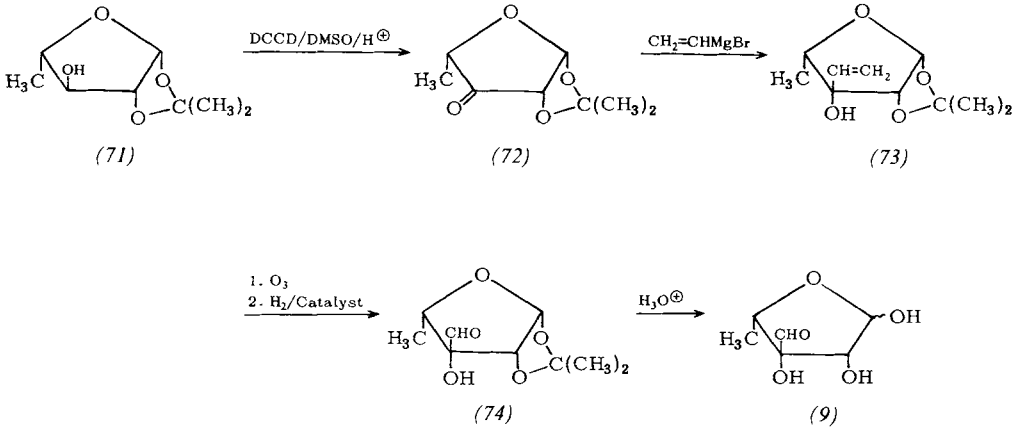
Whereas syntheses of the two basic components were achieved[37] by 1950, some fifteen years elapsed before a total synthesis (Scheme 8) of streptose [5-deoxy-3-*C*-formyl-L-lyxose, *(9)*] was reported[38], although its stereochemistry had been firmly established by other means[36].

Oxidation of 5-deoxy-1,2-*O*-isopropylidene-β-L-arabinofuranose *(71)*, using dicyclohexylcarbodiimide, pyridinium phosphate, and dimethyl sulfoxide (the Pfitzner-Moffatt reagent[15]), gave the ketone *(72)*, which underwent a stereospecific addition of vinylmagnesium bromide to yield 5-deoxy-1,2-*O*-isopropylidene-3-*C*-vinyl-β-L-lyxofuranose *(73)*. Catalytic hydrogenation of the ozonide of *(73)* gave the 3-*C*-formyl derivative *(74)*, which liberated streptose *(9)* on deacetonation with an acid resin.

2.6. Amicetose *(80)* and Rhodinose *(5)*

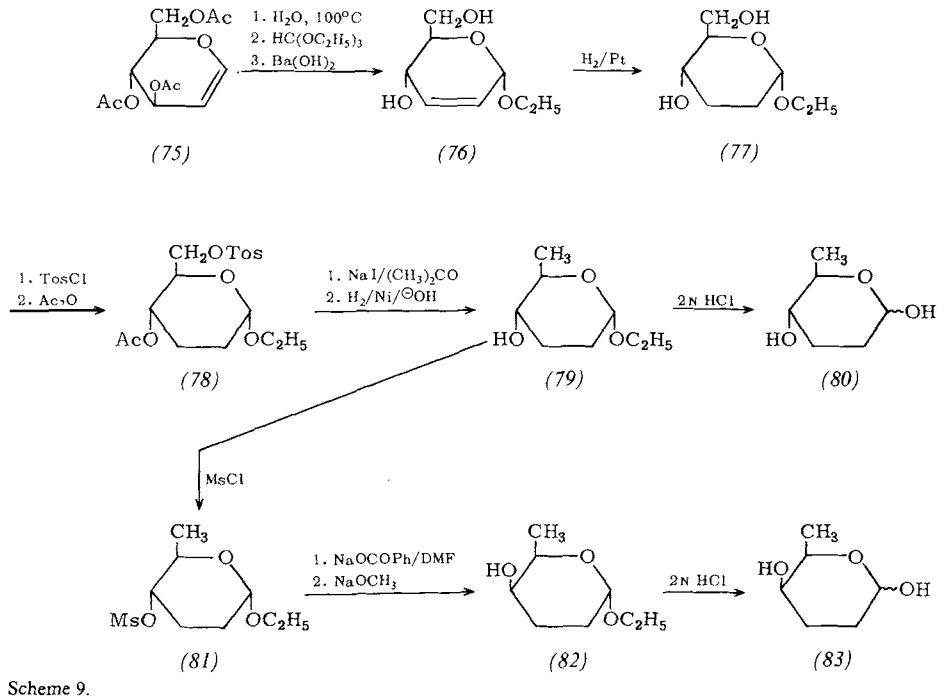
Both these sugars are 2,3,6-trideoxyaldohexoses. Amicetose [*(80)*, 2,3,6-trideoxy-α-D-*erythro*-hexose] is a constituent of the antibiotic amicetin[39], whereas rhodinose [*(5)*, 2,3,6-trideoxy-L-*threo*-hexose] is a constituent of rhodomycin[40] and streptolydigin[41]. The stereochemistry of amicetose was established by a synthesis[42] from the readily accessible D-glucal triacetate *(75)* (Scheme 9). The unsaturated sugar was transformed into ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[43] *(76)* which, after hydrogenation to the saturated glycoside *(77)*, was converted[42] into ethyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside *(79)* by way of the 6-*p*-toluenesulfonyl and 6-iodo derivatives. Acid hydrolysis of *(79)* afforded a trideoxyhexose *(80)* identical with amicetose.

The 6-deoxyglycoside *(79)* was also used[42] to confirm the stereochemistry of rhodinose, which had been assigned the L-*threo*-configuration *(5)* from optical rotatory data. Inversion of the configuration at C-4 by means of a benzoate displacement reaction on the derived methanesulfonate *(81)* gave, after debenzoylation, ethyl 2,3,6-trideoxy-α-D-*threo*-hexopyranoside *(82)*. The sugar *(83)* liberated on acid hydrolysis of *(82)* was recognized as the enantiomer of natural rhodinose *(5)*.



(71) *(72)* *(73)* *(74)* *(9)*

Scheme 8.

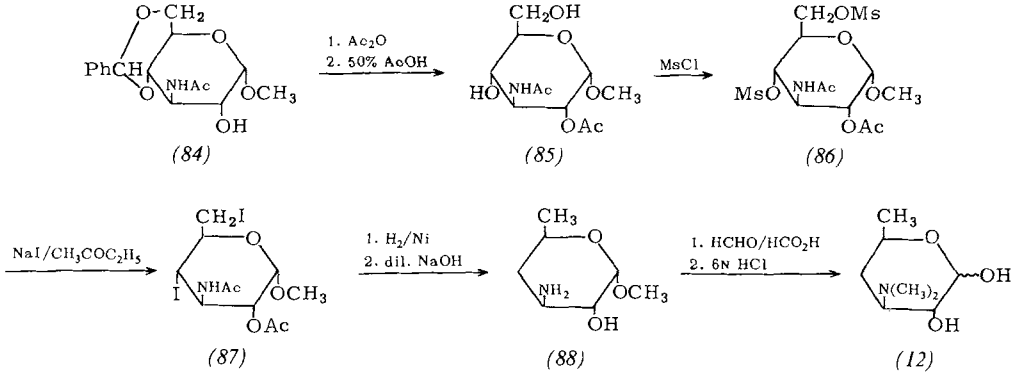


Scheme 9.

3. Antibiotic Amino Sugars

3.1. Desosamine *(12)*

The structure of desosamine was shown[44] by degradative and spectroscopic evidence to be 3,4,6-trideoxy-3-dimethylamino-D-*xylo*-hexose *(12)*. The glycosidically bound sugar is a component of several macrolide antibiotics such as erythromycin, narbomycin, picromycin, and oleandomycin. Non-specific syntheses of desosamine have been reported[45] but the stereospecific synthesis of desosamine outlined in Scheme 10 is due to *Richardson*[46].

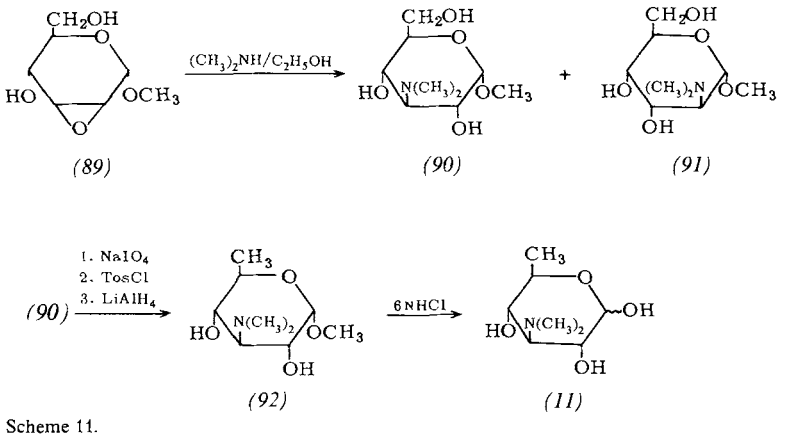


Scheme 10.

Partial acidic hydrolysis of the 2-acetate obtained by acetylation of methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-α-D-glucopyranoside[47] *(84)* converted it into the diol *(85)*. Treatment of the derived dimethanesulfonate *(86)* with sodium iodide in boiling butanone effected the displacement of *both* sulfonic ester groups to give a di-iodo derivative presumed to be *(87)*. Since secondary carbohydrate sulfonates are generally unreactive towards iodide ion under the conditions used, the displacement reaction undergone by *(86)* can be attributed to neighboring-group participation by the acetamido group and attack of iodide ion on the oxazoline intermediate. Hydrogenolysis of the di-iodide *(87)* over a nickel catalyst and deacetylation with strong base yielded methyl 3-amino-3,4,6-trideoxy-α-D-*xylo*-hexopyranoside *(88)*, which was converted into desosamine *(12)* following *N*-methylation, with the formic acid-formaldehyde reagent, and removal of the glycosidic substituent with acid.

3.2. Mycaminose *(11)*

This basic sugar is a component of antibiotics such as the leucomycins, the magnamycins, and members of the spiromycin group[5]. Mycaminose was identified[48] as a 3,6-dideoxy-3-dimethylaminohexose and, after some early



Scheme 11.

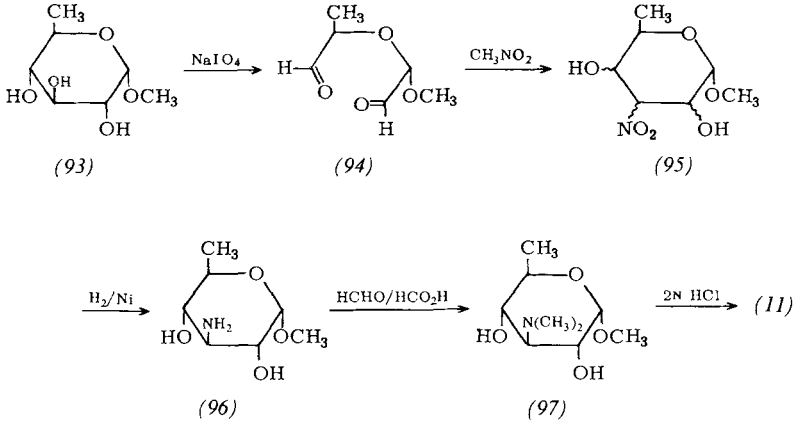
confusion, its absolute stereochemistry was finally decided by synthesis.

In the route used by *Foster et al.*[49] (Scheme 11), methyl 2,3-anhydro-α-D-allopyranoside *(89)* was heated with ethanolic dimethylamine to give an approximately equimolar mixture of the isomeric dimethylamino alcohols *(90)* and *(91)*. The D-*altro* isomer *(91)* was removed from the mixture by oxidation of the *vic*-diol system with sodium periodate and absorption of the resulting aldehydic fragment on to a strongly basic resin. The remaining D-*gluco* isomer *(90)* was converted, *via* the 6-*p*-toluenesulfonate, into the 6-deoxy derivative *(92)*, which was then hydrolyzed to 3,6-dideoxy-3-dimethylamino-D-glucose *(11)*. The hexosamine derivative—isolated as the hydrochloride monohydrate—was identical with natural mycaminose.

3.3. Perosamine *(13)*

4-Amino-4,6-dideoxyhexoses and their derivatives are constituents of a number of antibiotics[51]. The amino sugar component (perosamine) of the heptaenic antibiotic perimycin[52] was recognized[53] from chemical evidence as 4-amino-4,6-dideoxy-D-mannose *(13)*.

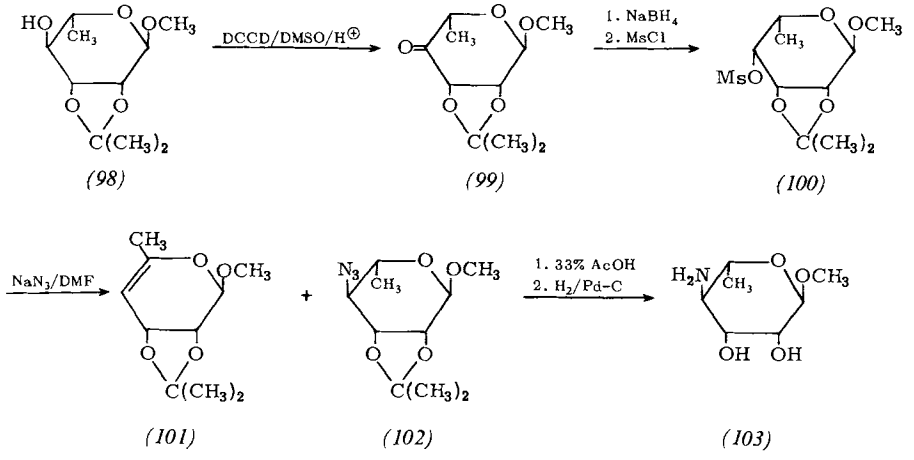
A relatively straightforward route to perosamine derivatives can be envisaged[51] by way of an azide displacement reaction on methyl 6-deoxy-2,3-*O*-isopropylidene-4-*O*-methanesulfonyl-α-D-talopyranoside *(100)*. An attempt to prepare the latter compound by a route involving nucleophilic displacements on the corresponding D-mannose sulfonate had to be abandoned when it was shown that ring-contracted products were formed[54].



Scheme 12.

In an alternative synthesis[50] (Scheme 12), the 3-amino function was introduced by nitromethane cyclization of the dialdehyde *(94)* formed on periodate oxidation of methyl 6-deoxy-α-D-glucopyranoside *(93)*. Methyl 3-amino-3,6-dideoxy-α-D-glucopyranoside *(96)* was isolated in 24 % yield following reduction of the mixture of isomeric 3-nitropyranosides *(95)*, and was further converted into the di-*N*-methyl derivative *(97)*. Subsequent hydrolysis of *(97)* with hydrochloric acid yielded mycaminose *(11)*.

This difficulty was overcome—in the L-series—by effecting the desired inversion of configuration through the ketone *(99)* (Scheme 13)[55]. Reduction of *(99)* with sodium tetrahydridoborate in methanol proceeded virtually stereospecifically to yield the L-*talo*-alcohol. Unfortunately, considerable amounts of the unsaturated sugar *(101)* accompanied the formation of the 4-azido derivative *(102)* in the reaction between the methanesulfonate *(100)* and sodium azide in dimethylformamide. However, the L-*manno*-amine *(103)*, resulting from partial



(98) (99) (100) (101) (102) (103)

Scheme 13.

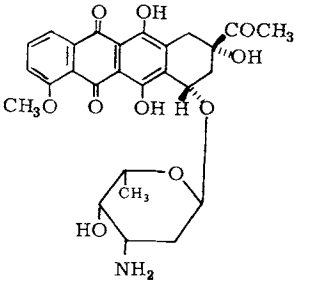
hydrolysis and catalytic hydrogenation of *(102)*, was shown to be enantiomeric with methyl perosaminide, obtained on methanolysis of the antibiotic[53].

Ring-opening of either methyl 3,4-anhydro-6-deoxy-α-D-talopyranoside or its 2-benzoate with lithium azide and ammonium chloride in 2-methoxyethanol has been used[56] to prepare derivatives related to natural perosamine.

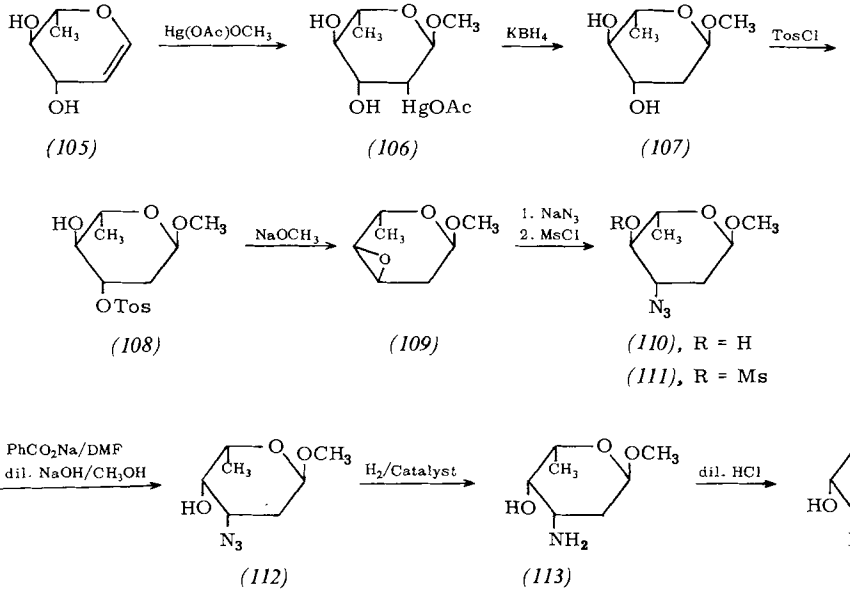
3.4. Daunosamine *(114)*

Daunomycin *(104)*[57] is a streptomyces metabolite possessing antitumor activity; the amino sugar component, named daunosamine[58], is 3-amino-2,3,6-trideoxy-L-*lyxo*-hexose *(114)*.

Two syntheses of D-daunosamine have been reported[59] but the quite elegant synthesis of *Goodman et al.*[60] yielded the natural L-sugar (Scheme 14). In this, methoxymercuration of L-rhamnal *(105)* provided an excellent route to the 2-deoxyglycoside *(107)*; the latter compound will also be recognized as the methyl glycoside of L-chromose C. Selective *p*-toluenesulfonylation of *(107)* gave the 3-sulfonate *(108)* which, after conversion into the epoxide *(109)*, was treated with sodium azide to yield the expected product, *viz.* methyl 3-azido-2,3,6-trideoxy-α-L-*arabino*-hexopyranoside *(110)*. A S_N2 displacement on the derived methanesulfonate *(111)* with sodium benzoate in dimethylformamide gave, after saponification of the ester group, methyl 3-azido-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside *(112)*. Catalytic reduction of *(112)* afforded the amino sugar glycoside *(113)*, which was hydrolyzed to daunosamine *(114)* with dilute hydrochloric acid.



(104)



(105) (106) (107) (108) (109) (110), R = H (111), R = Ms (112) (113) (114)

Scheme 14.

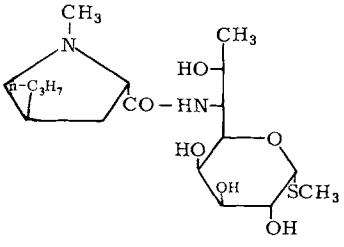
3.5. Garosamine *(17)*

Methanolysis of the antibiotic gentamicin C, a broad spectrum antibiotic complex isolated[61] from fermentations of *Micromonospora*, yielded[62] an amino sugar glycoside (methyl garosaminide), which was shown to be either methyl 3-deoxy-4-*C*-methyl-3-methylamino-β-L-arabinopyranoside or the corresponding α-D-*xylo* derivative. A decision in favor of the L-*arabino* isomer *(17)* was claimed[63] after the synthesis of derivatives related to both isomers (Scheme 15).

The readily accessible 3-amino-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[64] *(115)* was transformed[63] by standard reactions into the monoacetal *(116)*, which was subjected to a chain-shortening process with sodium periodate to give, after treatment with sodium tetrahydridoborate, the 3-aminoxylose derivative *(117)*. Deacetonation of *(117)* and acetalation of the free sugar using 2,2-dimethoxypropane afforded the corresponding pyranose acetal *(118)*, which was smoothly oxidized to the ketone *(119)* with ruthenium tetroxide in the presence of potassium periodate. A mixture of the two possible branched-chain sugars *(120)* was obtained on the addition of methylmagnesium bromide to *(119)*, which after methanolysis gave the glycosides *(121)* and *(122)*. The structures of these compounds were deduced by examining the extent of intramolecular hydrogen-bonding exhibited by the pure anomers in dilute solutions of carbon tetrachloride, and from nuclear magnetic resonance spectroscopy. The physical properties of a crystalline glycoside assigned the β-L-*arabino* configuration [*(121)*, β-form] were comparable with those of a similar garosamine derivative.

3.6. Lincosamine *(18)*

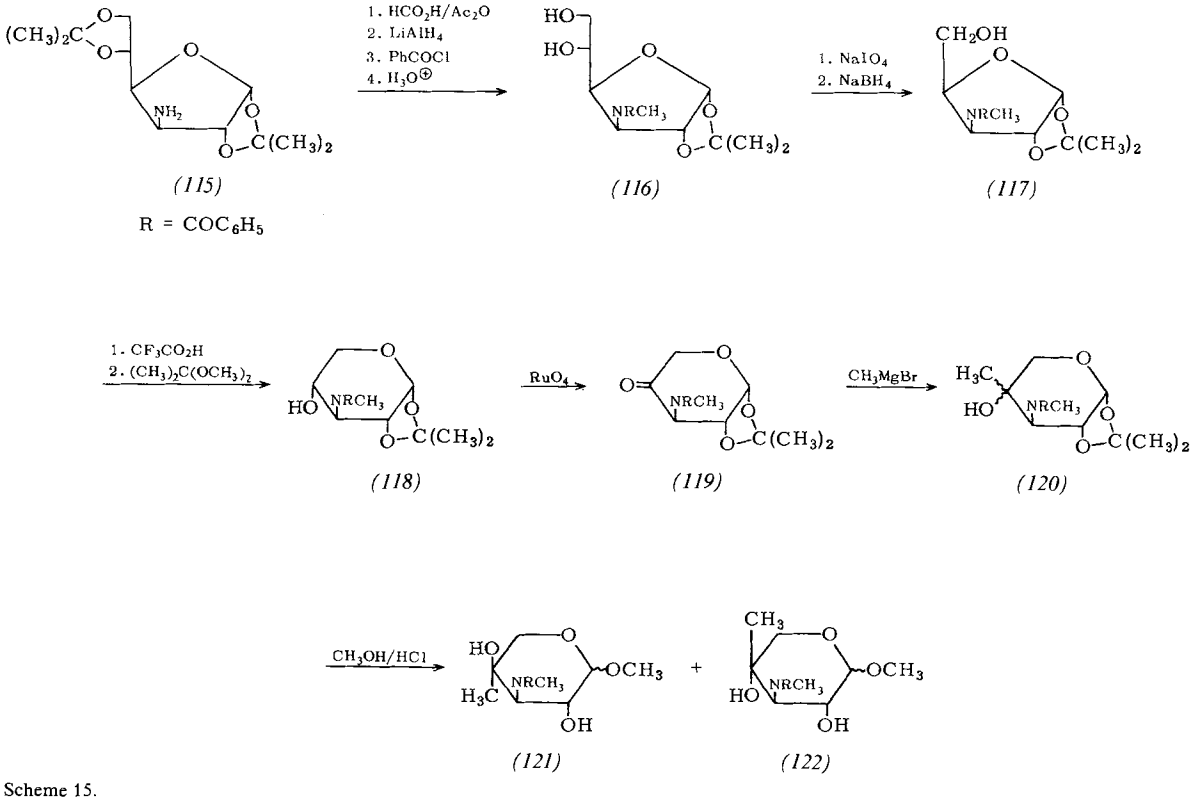
The antibiotic lincomycin *(123)*, produced by *Streptomyces lincolnensis* var. *lincolnensis*, is active against gram-positive organisms[65]. It consists[66] of the methyl thioglycoside of an aminodideoxyoctose (methyl 6-amino-6,8-dideoxy-1-thio-D-*erythro*-α-D-*galacto*-octopyranoside) bound by an amide linkage to an amino acid (*trans*-1-methyl-4-*n*-propyl-L-proline).



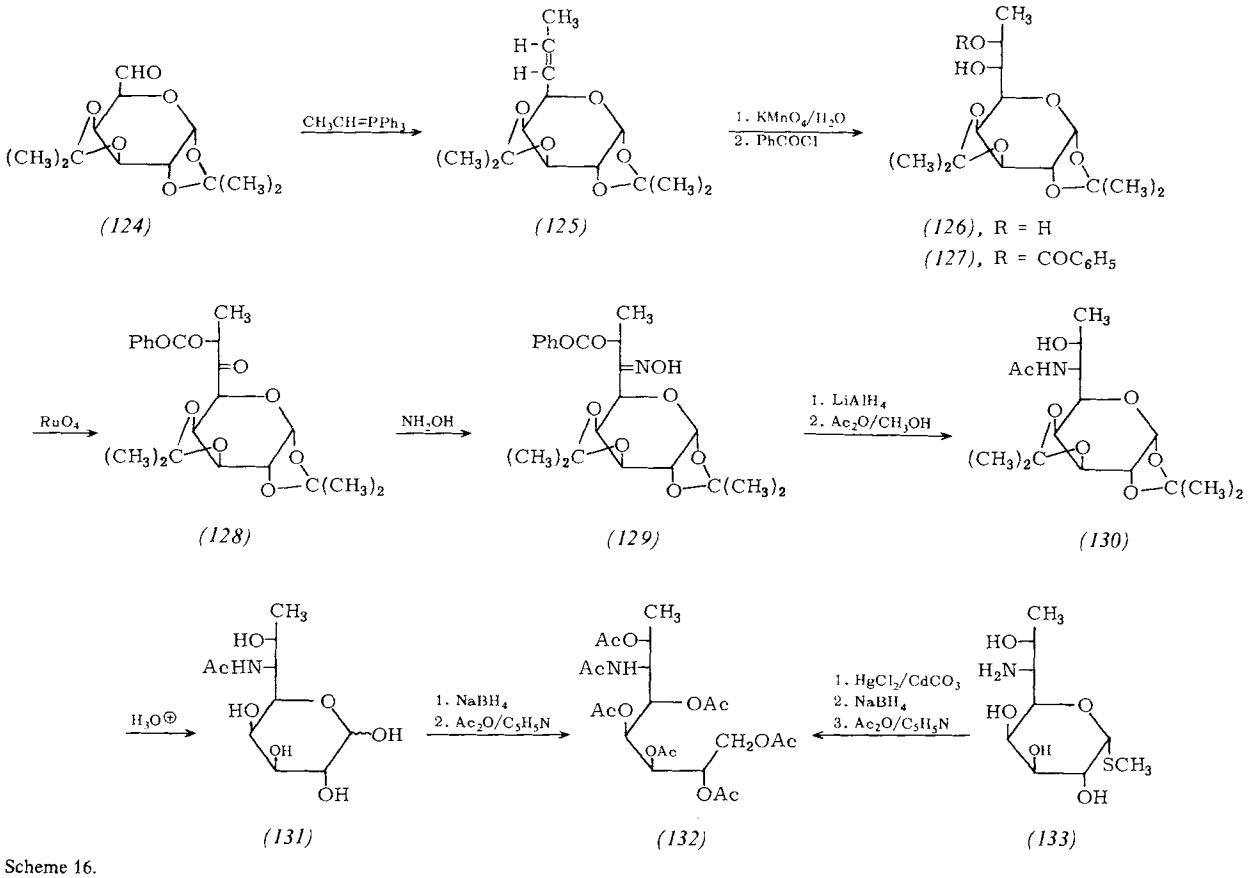
(123)

The main problem associated with the synthesis of lincosamine derivatives is the synthesis of the octose skeleton. This was achieved in a synthesis reported by *Howarth, Szarek*, and *Jones*[67] by means of a Wittig reaction between the D-galactose 6-aldehyde *(124)* and ethylidenetriphenylphosphorane. The resulting *cis*-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-oct-6-enose *(125)* was converted into the *cis*-diol *(126)* by hydroxylation with potassium permanganate (Scheme 16).

Selective benzoylation of *(126)* gave the monoester *(127)*, which was oxidized to the ketone *(128)* with ruthenium tetroxide. Oximation of *(128)* afforded a mixture of both isomeric oximes *(129)* from which one of the pure isomers



Scheme 15.

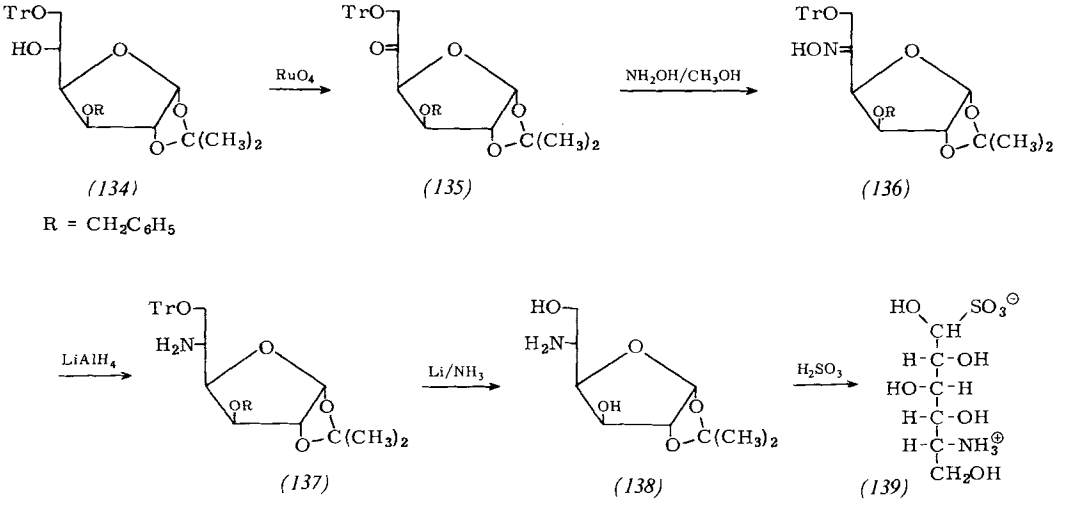


Scheme 16.

was obtained by fractional crystallization. Reduction of this oxime with lithium tetrahydridoaluminate gave, after *N*-acetylation, a mixture of *vic*-acetamido alcohols containing *(130)* as the major component. Partial hydrolysis of *(130)* liberated the free sugar *(131)* whose structural relationship with the antibiotic sugar was established by their mutual conversion into the heptaacetate *(132)*. In the case of methyl thiolincosaminide *(133)*, this required desulfurization with aqueous mercuric acetate and cadmium carbonate, sodium tetrahydridoborate reduction of the free sugar, and acetylation.

3.7. Nojirimycin *(16)*

Fermentation broths of several strains of *Streptomyces* yield an antibiotic nojirimycin[68], which is endowed with remarkable biological activity against *Sarcina lutea*, *Xanthomonas oryzae*, and *Shigella flexneri*. Chemical and spectroscopic evidence[69] clearly pointed to nojirimycin being D-glucopiperidinose *(16)*—that is, a sugar containing a nitrogen heteroatom in the six-membered ring [5-amino-5-deoxy-D-glucopyranose *(16)*].



Scheme 17.

The structure of nojirimycin was confirmed by a nine-stage synthesis[69] (Scheme 17) from D-glucose, which was initially converted into 3-*O*-benzyl-1,2-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-glucofuranose[70] *(134)*, and thence, on oxidation with dimethyl sulfoxide and acetic anhydride[116], into the 5-ketone *(135)*. Reduction of the oxime *(136)* derived from *(135)* over Raney nickel in ammoniacal methanol (or with lithium tetrahydridoaluminate in ether) yielded the diastereoisomeric 5-amino derivatives to which structures were assigned on the basis of optical rotatory dispersion measurements on their *N*-salicylidene derivatives. Treatment of the major isomer *(137)*, shown to have the D-*gluco* configuration, with lithium in liquid ammonia converted it into *(138)*, which was deacetonated with sulfurous acid. The sugar was intercepted as the bisulfite adduct *(139)*, and this was shown to be identical with the corresponding nojirimycin derivative; the free sugar *(16)* could be regenerated by hydrolysis of the adduct with a basic resin.

3.8. Paromose (Neosamine B) *(14)*

The antibiotics paromomycin and neomycin B contain a 2,6-diamino-2,6-dideoxyhexose (paromose) which, from chemical and biogenetic considerations, was indicated[71] to have the L-*ido* configuration *(14)*. This assignment of stereochemistry was verified when a MacDonald-Fischer degradation on *N,N*-diacetylparomose diethyl dithioacetal gave[72] 5-acetamido-5-deoxy-L-xylose. A synthesis of paromose has been described by *Meyer zu Reckendorf*[73].

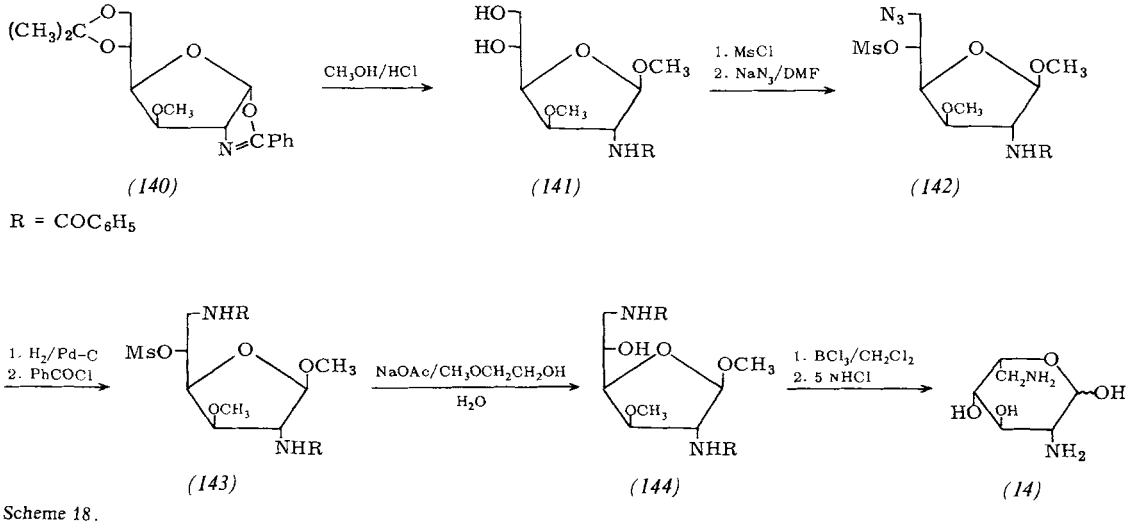
Careful treatment of the oxazoline[74] *(140)* (Scheme 18) with methanolic hydrogen chloride afforded methyl 2-benzamido-2-deoxy-3-*O*-methyl-β-D-glucofuranoside *(141)*, which gave the 6-azido-5-methanesulfonate *(142)* following treatment of the 5,6-dimethanesulfonate derivative with sodium azide in boiling dimethylformamide. Reduction of the azide group and *N*-benzoylation afforded methyl 2,6-dibenzoylamino-2,6-dideoxy-3-*O*-methyl-5-*O*-methanesulfonyl-β-D-glucofuranoside *(143)*, which underwent solvolysis to the L-idose derivative *(144)* in wet 2-methoxyethanol containing sodium acetate; the solvolysis is aided by participation of the neighboring benzoylamino group and results in inversion of configuration at C-5. Successive treatment of *(144)* with boron trichloride and dilute hydrochloric acid removed the protecting groups to give paromose *(14)*.

4. Future Developments

The constant search for new antibiotics continues to bring to light new sugars of unusual structure. The first naturally occurring nitro sugar (evernitrose) has been obtained[75] recently from everninomicin antibiotics, and the neutral macrolide aldgamycin E contains[76] two sugars, each possessing a cyclic carbonate group; the synthesis of these sugars presents a number of interesting problems. The challenge offered by the total synthesis of antibiotics that are entirely carbohydrate in nature has been accepted, and total syntheses of kanamycin A, B, and C were achieved[77] recently. Significant developments in this direction are likely to follow and, with a better understanding of the precise modes of action of these and related antibiotic substances, should lead to the synthesis of new and improved antibiotics.

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(140) R = COC_6H_5 *(141)* *(142)*

(143) *(144)* *(14)*

Scheme 18.

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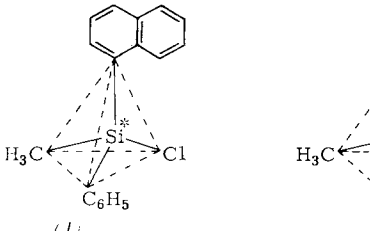
Optical Activity from Asymmetric Transition Metal Atoms

By Henri Brunner[*]

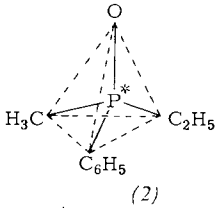
The preparation and resolution of asymmetric organometallic compounds of the transition series with four different ligands on the metal atom are described. Some of the optically active complexes retain their configuration, while others undergo racemization in solution. Their properties and reactions are discussed. Centers of asymmetry at transition metal atoms can also be detected on the basis of the magnetic nonequivalence of diastereotopic groups. Information about the configurational stability of such compounds can be obtained by investigation of the temperature dependence of the nuclear magnetic resonance spectra.

1. Introduction

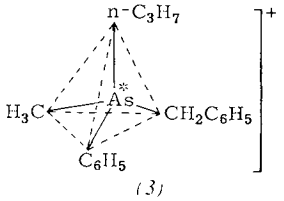
Compounds containing an asymmetric carbon atom C(a, b, c, d) can generally be resolved into enantiomers[1,2]. This is also true of other main-group elements, such as beryllium[3,4], boron[3,5], silicon[6-8], germanium[9-11], nitrogen[12,13], phosphorus[12,15-17], and arsenic[12,16], when they are situated at the center of a tetrahedron with four different substituents, as shown in the examples *(1)*[7],



(1)



(2)

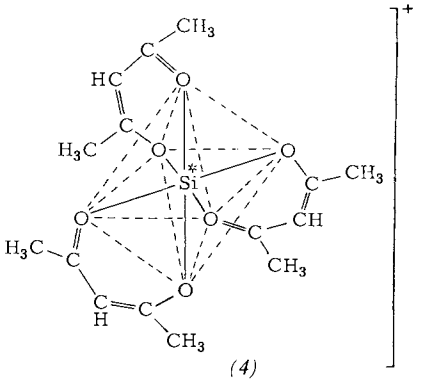


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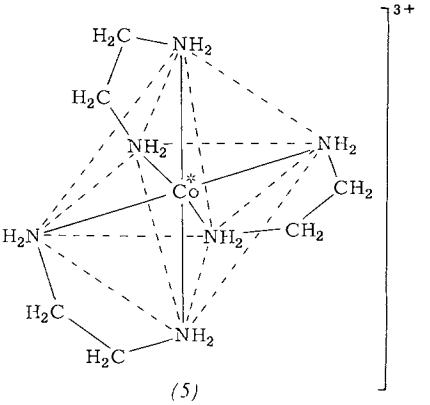
(2)[15,17], and *(3)*[16,18]. For compounds where optical activity has been measured, an asterisk marks the center of asymmetry in the present article. Only a few octahedral compounds of main-group elements have been obtained in optically active forms[19,20], an example being the cation $[Si(acac)_3]^+$ *(4)*[21].

On the other hand, there are many optically active octahedral chelates of transition metals[19,20]. The cobalt cations *(5)*[22-24] and *(6)*[25,26], which were isolated in the pioneering studies of *A. Werner*, are typical of this class of compound. However, optically active derivatives with tetrahedral structures are confined to a few complexes[27-30] of symmetry C_2 of the type *(7)* with unsymmetrical chelate ligands[27].

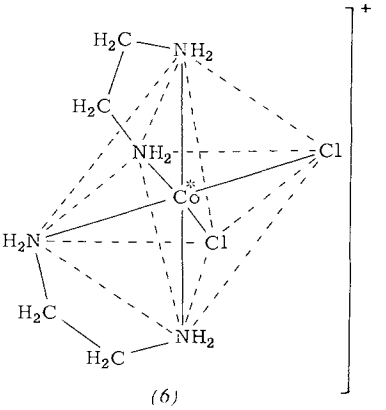
Chiral optically active transition metal compounds with four different substituents $M(L_1, L_2, L_3, L_4)$ *(8a)* and *(8b)*, corresponding to the optically active organic compounds with asymmetric carbon atoms, were previously unknown. Our aim was to prepare tetrahedral transition metal complexes $M(L_1, L_2, L_3, L_4)$ containing four different ligands, to separate the optical antipodes *(8a)*



(4)



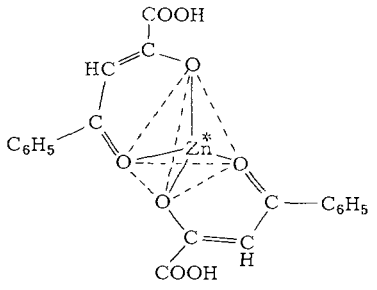
(5)



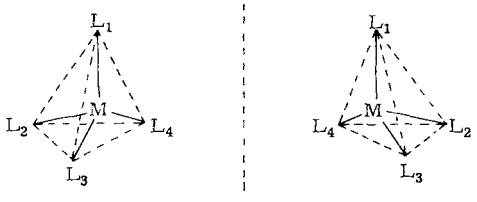
(6)

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and *(8b)* of these compounds, and to carry out reactions with the optically active complexes in order to establish their stereochemical course.



(7)



(8a) *(8b)*

Either *cis-trans* isomers or enantiomers may be used for the investigation of the stereochemistry of substitutions of *octahedral* complexes. Information about the steric course of the reaction can be obtained from the structure of the end products. Only *cis-trans* isomers can be used in the case of *square-planar* complexes, since compounds of this type do not occur in optically active forms. *Tetrahedral* compounds, on the other hand, do not exhibit *cis-trans* isomerism. Only optically active derivatives are therefore available in this case for the investigation of the stereochemistry of substitutions. The manner in which these can be used for the elucidation of reaction mechanisms is shown by the classic investigations of *Ingold* and *Hughes* on nucleophilic substitutions on the sp^3-hybridized carbon atom[31] and by more recent work on reactions of silicon-[6] and phosphorus compounds[14]. Similar stereochemical results should be obtainable from the investigation of optically active tetrahedral transition metal compounds. The comparison of substitution reactions of tetrahedral compounds of main group elements and transition metals looks particularly interesting.

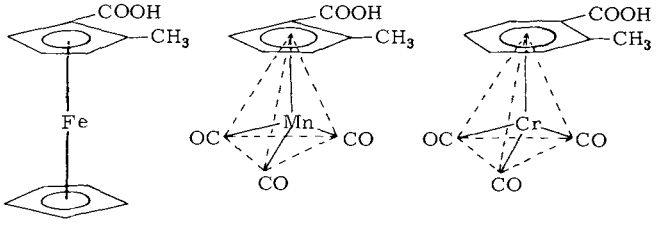
There are two main difficulties to be overcome in the preparation of tetrahedral transition metal complexes $M(L_1, L_2, L_3, L_4)$. Firstly, there are no suitable synthetic methods available by which complexes of this type can be "made to measure", as is possible in the case of organic compounds. Secondly, complexes of the type *(8a)* and *(8b)* are often kinetically unstable; they disproportionate with formation of a mixture of all possible products, as follows:

$$M(L_1, L_2, L_3, L_4) \rightarrow M(L_1)_4 + M(L_2)_4 + \cdots + M(L_1)_3L_2 + \cdots \quad (1)$$

"Scrambling" reactions of this kind have already been observed for many compounds of main group and transition elements containing several different ligands[32].

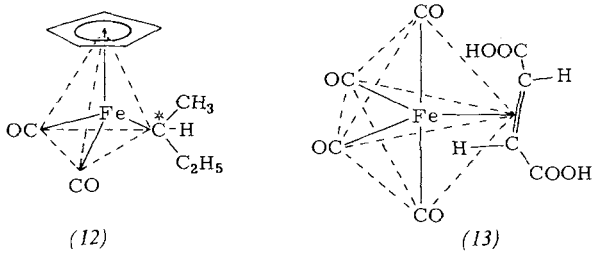
Organometallic compounds seem particularly suitable as a means of avoiding these difficulties, since the synthetic possibilities are greatest in this field of inorganic chemistry. Moreover, the σ-donor bonds from the ligands to the metal atom are strengthened in organometallic compounds by additional π back-bonding from the metal atom to empty antibonding orbitals of the ligands. This interaction of σ-donor and π-acceptor bonds should lead to a relatively stable bond framework, which should rule out disproportionation reactions in accordance with equation (1). This is essential for the isolation and subsequent resolution of derivatives with four different substituents.

Optically active organometallic compounds of the transition series are in fact known, examples being derivatives of ferrocene[33–36], cyclopentadienyltricarbonylmanganese[33,36,38], and benzenetricarbonylchromium[33,39–41] with different substituents in positions 1 and 2 of the same ring, such as *(9)*[36], *(10)*[37,38], and *(11)*[37,41]

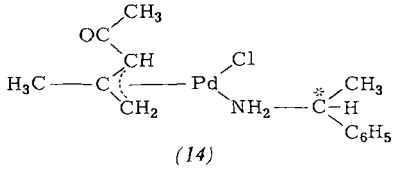


(9) *(10)* *(11)*

Unlike in the compounds $M(L_1, L_2, L_3, L_4)$ *(8a)* and *(8b)*, however, the metal atom is not the center of asymmetry in the complexes *(9)–(11)* or in the optically active alkyl-[42], olefin-[43–46], and allyl derivatives[47,48], *(12)*[42], *(13)*[44,45], and *(14)*[47,48]. The optical activity of these



(12) *(13)*

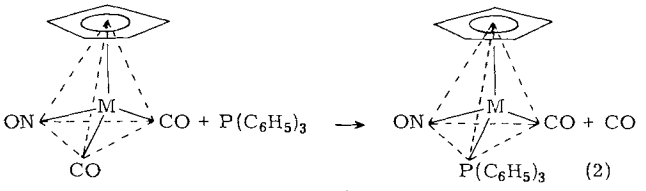


(14)

complexes is due to the dissymmetry of the ligands, and particularly their asymmetric C atoms. The plane of symmetry that is still present in the free ligands is lost on complex formation, and the compounds *(9)–(11)*, *(13)*, and *(14)* are therefore also described as exhibiting planar chirality[49].

2. Preparation of Transition Metal Complexes Containing Four Different Substituents

The cyclopentadienyldicarbonylnitrosyl complexes *(15)* of chromium, molybdenum, and tungsten[50] are readily obtainable compounds that already contain three different ligands. In the reaction of these compounds with triphenylphosphane, a CO group is replaced by the phosphane in accordance with



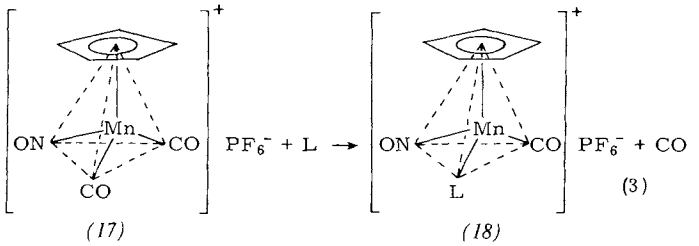
(15) *(16)* (2)

M = Cr, Mo, W

and the monosubstitution products *(16)* with four different ligands on the metal atom are formed[51,52]. On substitution of the strong π acceptor CO by triphenylphosphane, the electron density on the metal atom increases, with the result that the M→C back-bonding to the remaining CO group is strengthened. The CO ligand in *(16)* is consequently much more strongly bound, and hence more difficult to replace, than the CO ligands in *(15)*. The reaction therefore stops at the monosubstitution stage, even when an excess of triphenylphosphane is used[51].

It is usually assumed that the π-cyclopentadienyl ligand occupies three coordination positions on the metal atom. The compound *(16)* should therefore be classified as octahedral, and not as pseudotetrahedral. This view is not without its opponents[53]. However, since there are only four ligands on the metal atom, complexes of the type $C_5H_5M(L_1, L_2, L_3)$ only have the stereochemical possibilities of the tetrahedron, *i.e.* two opposite configurations, irrespective of how the cyclopentadienyl group is bonded.

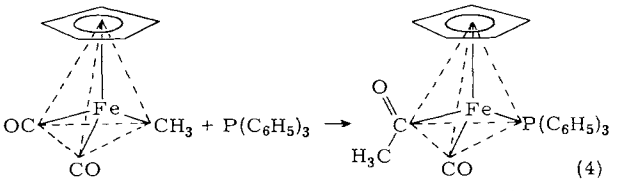
Substitution experiments on $[C_5H_5Mn(CO)_2NO][PF_6]$[54,55] *(17)* have shown that the CO groups of the cation are more readily replaced by other ligands than those of the isoelectronic neutral complex $C_5H_5Cr(CO)_2NO$[56,57]. This is due to the positive charge of the Mn complex, which prevents strong back-bonding from the metal atom to the carbonyl groups. The CO ligands are therefore only loosely bound, and can be readily replaced by many donors L such as phosphanes, phosphites, arsanes, and isocyanides, in accordance with



(17) *(18)* (3)

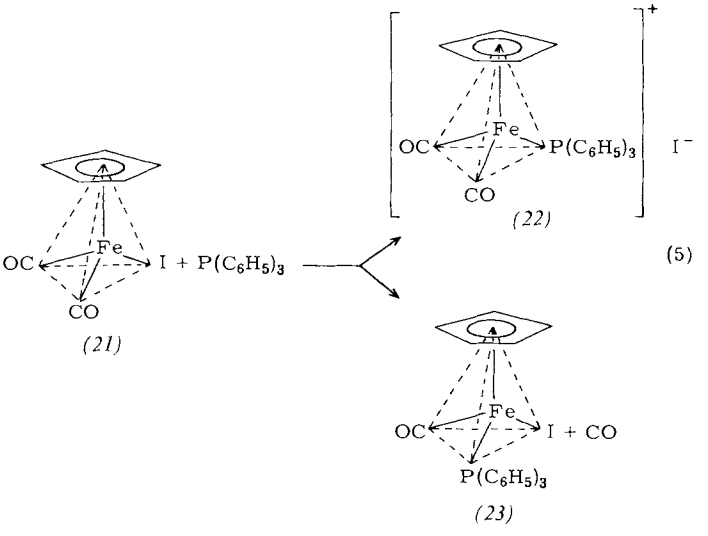
The monosubstitution products *(18)* are formed in this way at room temperature, and also the corresponding disubstitution products at higher temperatures[56-59]. However, the reaction can easily be stopped at the monosubstitution stage; this gradation of reactivity is a great help in the attempt to prepare transition metal complexes with four different substituents.

We have carried out these substitutions to obtain asymmetric complexes for resolution of the racemates. However, other reactions yielding compounds with four different ligands have also been described, though these were not used for stereochemical purposes. For example, cyclopentadienyldicarbonylmethyliron *(19)* reacts with triphenylphosphane in accordance with equation (4)[60,61].



(19) *(20)* (4)

The methyl group migrates from the iron atom on to the carbon atom of a carbonyl ligand to form an acetyl group in *(20)*. In the reaction of cyclopentadienyldicarbonyliodoiron *(21)*



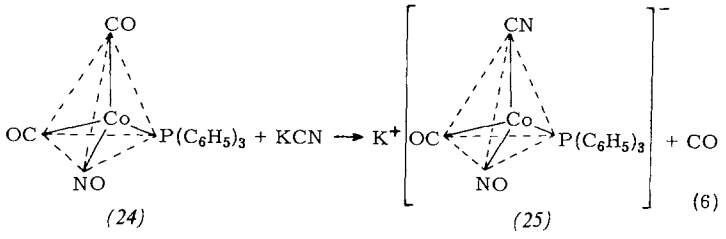
(21) *(22)* *(23)* (5)

the ligands CO and I^- are replaced to roughly equal extents by triphenylphosphane[61]. The compound *(23)* formed on replacement of the CO also contains four different substituents on the iron atom.

The reaction of the readily obtainable complex *(24)*[62] with KCN yields the potassium salt of the carbonylnitrosyltriphenylphosphanecyanocobaltate ion *(25)*[63].

It can be seen from these examples that four different substituents can readily be incorporated into approximately tetrahedral molecules by the synthetic methods of organometallic chemistry, and that the products, with few exceptions[64], are kinetically stable and do not disproportionate in accordance with equation (1).

As has been predicted many times[63, 65–67], it should be possible to separate the enantiomers of compounds of the type *(16)*, *(18)*, *(20)*, *(23)*, and *(25)*. However,



(24) *(25)* (6)

attempts to achieve such a separation with the anion of the salt *(25)* have so far been unsuccessful[67]. We shall now show how the examples of equations (2)–(6), stereochemically modified, can be used for the resolution of racemates or for the NMR-spectroscopic detection of centers of asymmetry on the metal atom.

3. Diastereoisomeric Manganese Complexes

In the compound cyclopentadienylcarbonylnitrosyltriphenylphosphanemanganese hexafluorophosphate *(26a,b)*[56–59], the manganese atom is approximately tetrahedrally surrounded by four different ligands. The complex cations therefore occur in pairs of enantiomers, each being 50% in the D configuration and 50% in the L configuration. The symbols D and L are used only to distinguish the two opposite configurations. On reaction with an optically active component, enantiomers are converted into diastereoisomers which have different physical and chemical properties[1, 2]. A very suitable optically active substance in this case is the anion of the naturally occurring alcohol menthol, to which we shall assign the configuration L. The mentholate ion adds to the carbonyl carbon of the complex cation[68] to form an ester group. The product consists of the pair of diastereoisomers D,L/L,L *(27a,b)*. The two diastereoisomers *(27a)* and *(27b)* can be separated on the basis of their solubility differences. Whereas the dextrorotatory compound *(27a)* is soluble in pentane, the levorotatory *(27b)* is only sparingly soluble[68].

Both complexes are configurationally stable in the solid state; their optical rotations do not change at room temperature[68]. In solution, on the other hand, both *(27a)* and *(27b)* lose their high rotation values in a matter of hours. The equilibrium (8) is established between the two forms, since the configuration on the manganese atoms changes in solution[68, 73]. From both sides, the rotation reaches a constant equilibrium value $[\alpha_\infty]^{25}_{579} = +90°$ in benzene solution.

The diastereoisomers *(27a)* and *(27b)* can be interconverted by means of the equilibrium (8) if the different solubilities are taken into account. For example, when the more readily soluble dextrorotatory *(27a)* is heated in pentane, the sparingly soluble levorotatory *(27b)* eventually separates out in the pure state[68].

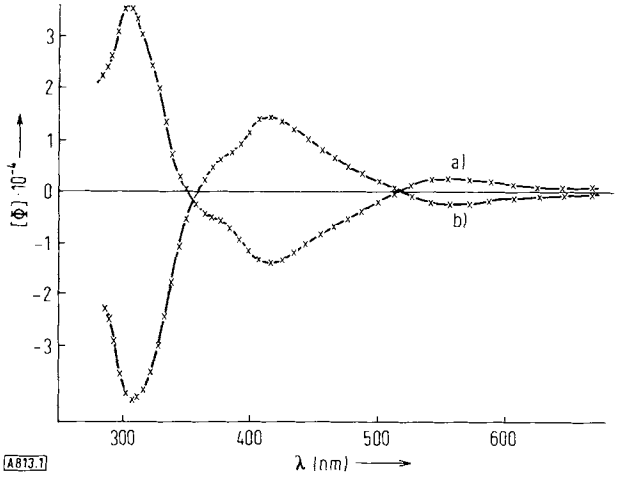
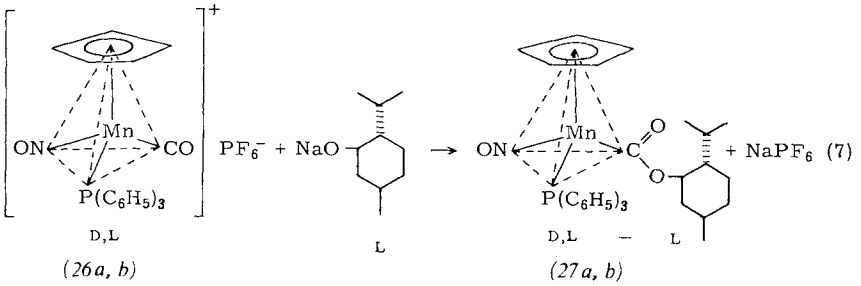
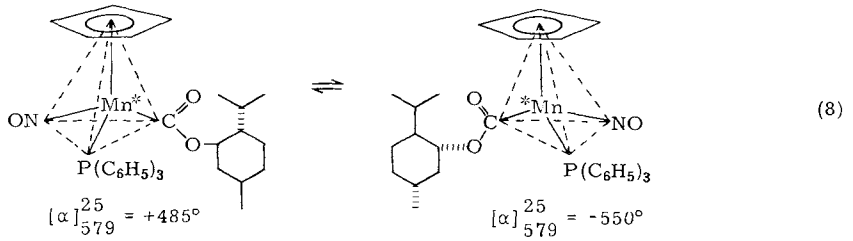


Fig. 1. ORD spectra of (a) *(27a)* and (b) *(27b)* in benzene.

The ORD and CD spectra of *(27a)* and *(27b)* are shown in Figures 1 and 2. Both compounds contain the same L-menthyl residue, but this does not absorb above 300 nm.



(26a, b) *(27a, b)*



(27a) *(27b)* (8)

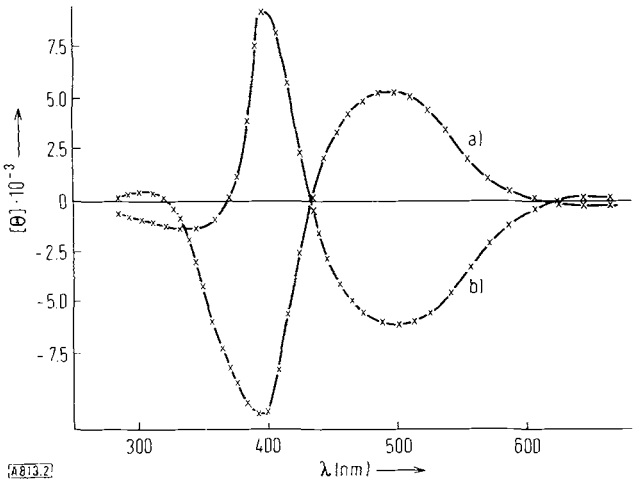


Fig. 2. CD spectra of (a) *(27a)* and (b) *(27b)* in benzene.

The bands in this region are therefore due only to the metal chromophore and its interaction with the ligands. Since the metal atoms in *(27a)* and *(27b)* have opposite configurations, the ORD and CD curves obtained are approximate mirror images.

4. Enantiomeric Manganese Complexes

The preparation of the diastereoisomeric manganese compounds *(27a)* and *(27b)* from the racemic mixture of $[C_5H_5Mn(CO)(NO)P(C_6H_5)_3][PF_6]$ *(26a,b)* was described in Section 3. To complete the resolution of the racemate, the added optically active component, *i.e.* the mentholate ion, must be removed from the diastereoisomers *(27a)* and *(27b)*. This can be achieved by reaction with acids, which allows the removal of alkoxide from ester groups bonded to metals[69, 70].

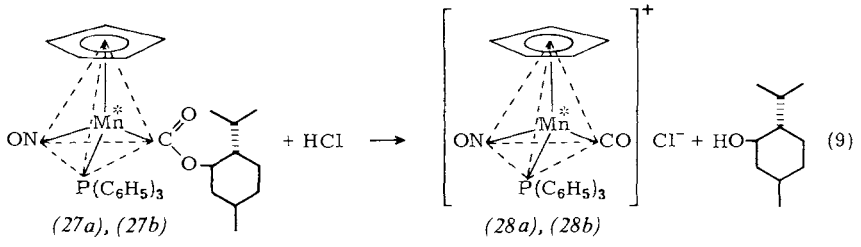
If dry HCl is passed through solutions of the neutral ester derivatives *(27a)* and *(27b)* in toluene, preferably at −20 °C to prevent epimerization, the chlorides of the cyclopentadienylcarbonylnitrosyltriphenylphosphanemanganese cations *(28a)* and *(28b)* precipitate out within a few minutes[71]. The menthyl residue is eliminated in this way. The chlorides can be converted with NH_4PF_6 into the water-insoluble hexafluorophosphates *(26a)* and *(26b)*[71].

These reactions are stereospecific. The dextrorotatory diastereoisomer *(27a)* gives the (+) form of the salt *(26a)*, while the levorotatory *(27b)* gives the (−) form of the salt *(26b)*[71]. Since the reaction with HCl only involves the ligands, it does not affect the centers of asymmetry at the metal atoms. Both the two dextrorotatory compounds *(26a)* and *(27a)* and the two levorotatory compounds *(26b)* and *(27b)* therefore have the same relative configuration at the manganese atom[71]. The optical rotation values of the salts *(26a)* and *(26b)* agree except in sign to within the limits of accuracy, as is to be expected for enantiomers.

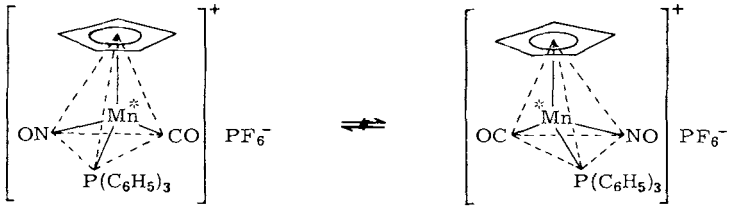
The optical activity of the diastereoisomers *(27a)* and *(27b)* is partly due to the three asymmetric carbon atoms in the menthyl residue. The salts *(26a)* and *(26b)*, on the other hand, no longer contain any asymmetric carbon atoms. Their optical activity is therefore entirely due to asymmetric metal atoms[71].

Unlike the diastereoisomers *(27a)* and *(27b)*, which epimerize in solution, the salts *(26a)* and *(26b)* are found to be configurationally stable. Their solutions in methylene chloride or tetrahydrofuran show no decrease in the rotation values on storage for several weeks even above room temperature[71]. There is also no change in the rotation values in the presence of an excess of triphenylphosphane. Backside attack of triphenylphosphane, which should lead to racemization by formation of S_N2-like transition states, therefore does not occur[71].

The optically active salts *(26a)* and *(26b)* can be used for the synthesis of other optically active compounds. For example, the reaction with sodium methoxide leads in accordance with the route shown in equation (10)

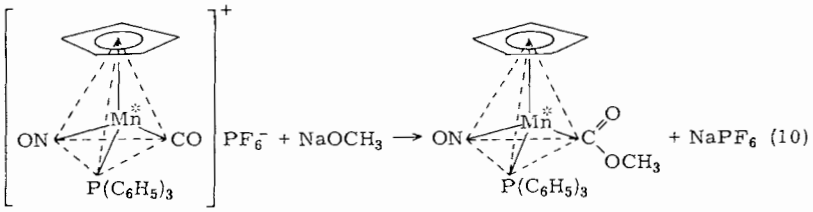


(27a), (27b) *(28a), (28b)*



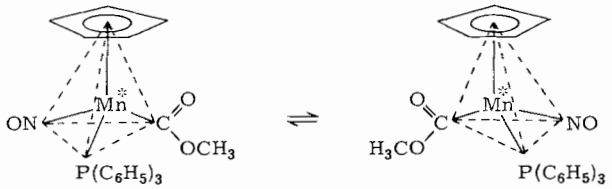
$[\alpha]_{579}^{25} = +375°$ *(26a)*

$[\alpha]_{579}^{25} = -386°$ *(26b)*



(26a), (26b) (29a), (29b)

(10)



$[\alpha]_{579}^{25} = +550°$ (29a)

$[\alpha]_{579}^{25} = -530°$ (29b)

(11)

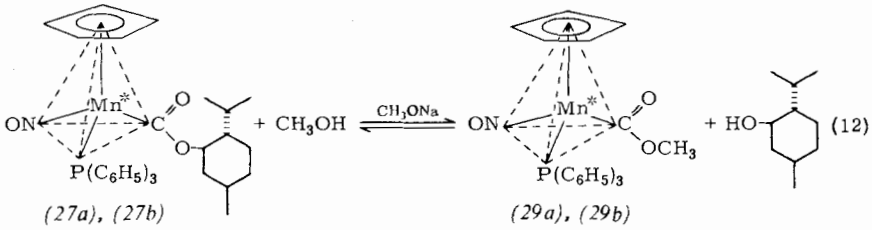
to the neutral methyl esters *(29a)* and *(29b)*[72]. The dextrorotatory *(26a)* yields the (+) form *(29a)*, and the levorotatory *(26b)* the (−) form *(29b)*. A mirror-image relation is again found for the rotation values of the optical antipodes[72].

The same methyl esters *(29a)* and *(29b)* are obtained by the action of sodium methoxide on the menthyl esters *(27a)* and *(27b)* in methanol.

With methanol as the solvent, the equilibrium is completely displaced to the side of *(29a)* and *(29b)*[72]. The dextrorotatory diastereoisomer *(27a)* is converted in this reaction into the dextrorotatory methyl ester *(29a)*, and the levorotatory diastereoisomer *(27b)* into the levorotatory methyl ester *(29b)*[72].

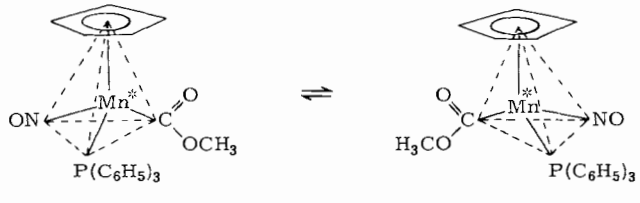
(29a) and *(29b)* are configurationally stable in the solid state[72]. The racemization that occurs in solution can be investigated kinetically. The rotation values fall off exponentially with time from both sides, and ultimately reach 0 (Fig. 3)[73]. A plot of the logarithm of $[\alpha_t]$, *i.e.* rotation value at time *t*, against time yields a straight line whose slope can be used to find the rate constant for the approach to racemization equilibrium. The decrease in the rotation value is a first order reaction with a halflife of 170 min at 30 °C in benzene solution. The activation energy for the racemization is 31.1 kcal/mole, the entropy of activation 21.8 e. u.

Intramolecular and intermolecular mechanisms are conceivable for the change in configuration on the manganese atom. Highly positive values for the entropy of activation in reactions of organometallic compounds in nonpolar solvents are generally regarded as indicative of a dissociative mechanism[74, 75]. The activation parameters thus favor an intermolecular mechanism[73] such as (13).



(27a), (27b) (29a), (29b)

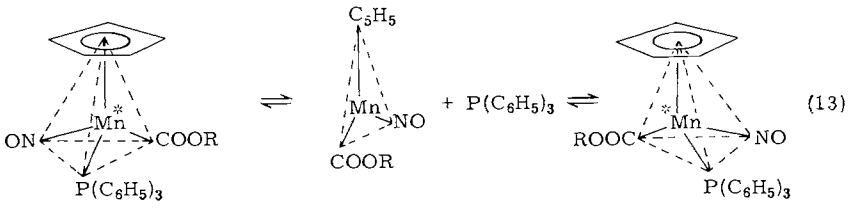
(12)



$[\alpha]_{579}^{25} = +550°$ (29a)

$[\alpha]_{579}^{25} = -530°$ (29b)

(11)



(29a) *(29b)*

Metal-cyclopentadienyl and metal-nitrosyl bonds are generally not broken at room temperature in complexes such as *(29a)* and *(29b)*. Also the fission of the ester-to-metal bond would lead to either energy-rich ions or radicals. Only the removal of triphenylphosphane in accordance with equation *(13)* gives a stable ligand molecule together with the coordinatively unsaturated

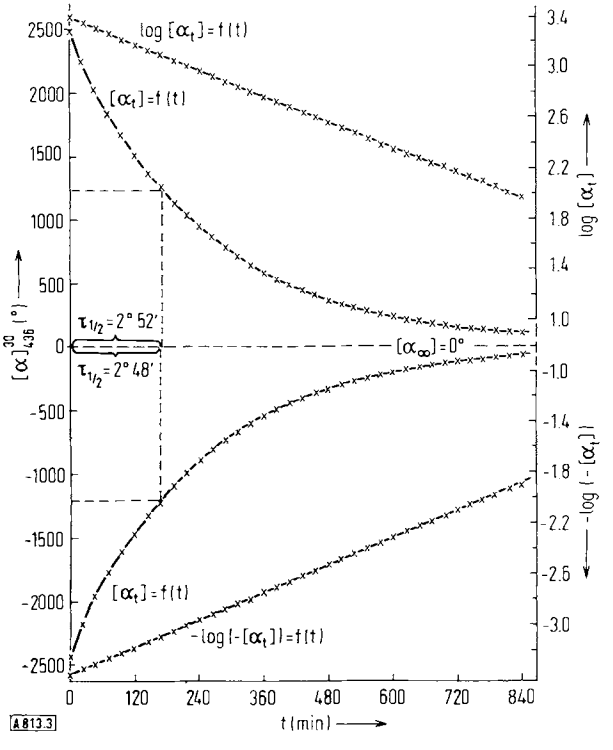


Fig. 3. Optical rotation values $[\alpha_t]$ of *(29a)* and *(29b)* as a function of time at 30 °C in benzene (left ordinate); log $[\alpha_t]$ as a function of time (right ordinate).

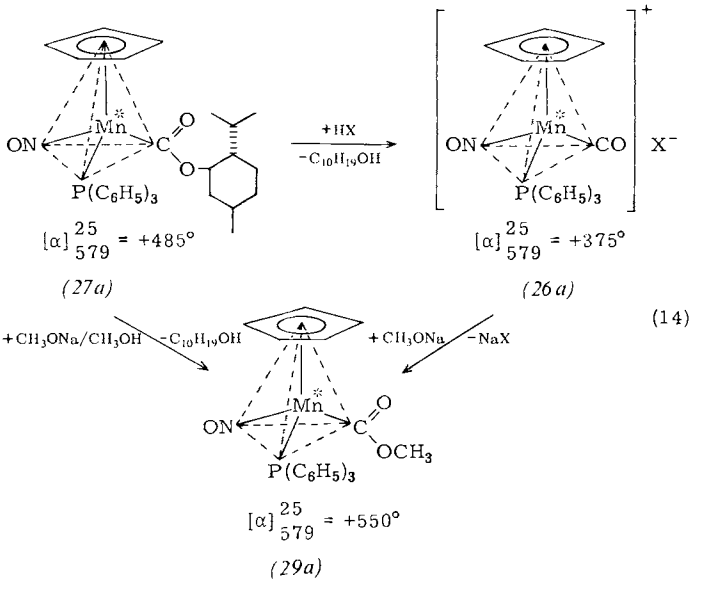
metal complex that is formed in every case. Since dissociations of $P(C_6H_5)_3$ from transition metal complexes are known[76], the cleavage of the Mn—P bond is the most likely process for the change in the configuration on the manganese atom[73], which must be the basis not only of the racemization of *(29a)* and *(29b)* but also of the epimerization of *(27a)* and *(27b)*.

The enantiomeric methyl derivatives *(29a)* and *(29b)* are of the same type as the menthyl derivatives *(27a)* and *(27b)*. A comparison of these compounds, which differ only in the alkyl residue of the ester group, should give an indication of whether electronic or steric effects are responsible for the change in configuration on the manganese atom. The electronic effects of the different OR groups on the cleavage of the Mn—P bond, which is some distance away in the molecule, should be approximately equal, whereas the steric effects of methyl and menthyl residues are very different. The menthyl group is much more bulky than the methyl group, particularly because of the isopropyl residue in position 2.

Kinetic measurements give almost the same results for the menthyl compounds *(27a)* and *(27b)* as for the methyl compounds *(29a)* and *(29b)*.

It may therefore be concluded that the steric effects do not play a very important part in the racemization. Whether the Mn—P bond is broken therefore depends mainly on the electron density on the metal atom.

Six optically active compounds have so far been prepared in the manganese series. The three dextrorotatory complexes *(26a)*, *(27a)*, and *(29a)* can be converted into one another, as indicated in scheme (14), as can the three levorotatory complexes *(26b)*, *(27b)*, and *(29b)*. Since these reactions involve only the ligands, both the dextrorotatory and the levorotatory complexes form series



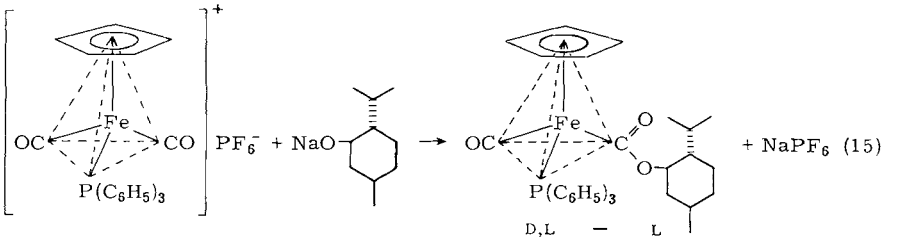
with the same relative configuration on the manganese atom. The configurations *(27)* and *(29)* are labile; the products racemize in solution. The configurations *(26)* are stable; the optical rotation values of the complexes do not change in solution.

5. Diastereoisomeric Iron Complexes

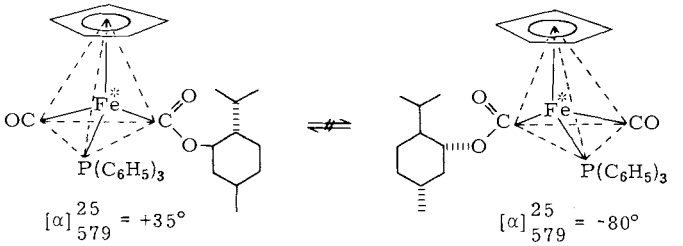
Cyclopentadienyldicarbonyltriphenylphosphaneiron hexafluorophosphate *(30)*[61] serves as the starting material for another series of optically active organometallic com-

pounds. The cation in *(30)* is not chiral, since it contains two CO ligands, and hence a plane of symmetry. On addition of the mentholate ion to one of the two CO groups in accordance with equation (15), however, a center of asymmetry is produced at the iron atom[77].

Transesterification of the diastereoisomeric iron-menthyl compounds *(31a)* and *(31b)* in methanol should, as in the case of the manganese complexes *(27a)* and *(27b)*, lead to optically active enantiomeric iron-methyl derivatives. As is shown in scheme (16), however, the racemized



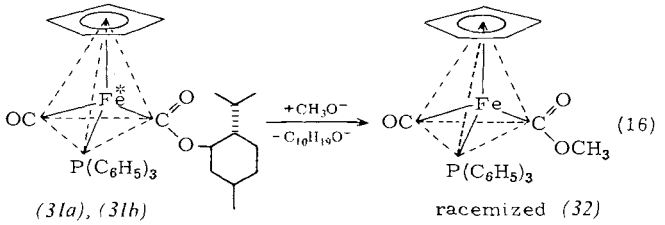
(30) *(31a, b)*



(31a) *(31b)*

The pair of diastereoisomers *(31a,b)* can again be resolved into the pure dextrorotatory and levorotatory diastereoisomers *(31a)* and *(31b)* on the basis of solubility differences[77]. The rotation values of the two complexes are very strongly dependent on temperature[78].

The iron compounds *(31a)* and *(31b)* correspond to the manganese complexes *(27a)* and *(27b)* according to the "nitrosyl shift principle"[79]. If the central metal in a compound is replaced by the element before it in the Periodic Table, which contains one electron less, while a CO ligand is simultaneously replaced by a NO ligand, which supplies one electron more, the same compound type is obtained. The similarity of the compounds *(27)* and *(31)*, which are analogous according to the nitrosyl shift principle, is so extensive that their IR spectra practically coincide apart from the differences in the CO and NO vibrations[78]. However, they differ in one other respect. The iron compounds are configurationally stable not only in the solid state but also in benzene solution[77], whereas the corresponding manganese derivatives racemize at room temperature with half lives of 2–3 hours[68,73].



(31a), (31b) racemized *(32)*

methyl ester *(32)* is always formed[78]. On dissolution of *(31a)* and *(31b)* in methanol, the optical activity decreases within a few seconds to the value for free menthol, and the racemized complex *(32)* separates out[78], whereas solutions of the complexes *(31a)* and *(31b)* in benzene do not lose their optical activity[77].

The transesterification of the manganese complexes *(27a)* and *(27b)* in accordance with equation (12), unlike that of the iron complexes *(31a)* and *(31b)*, does not take place in pure methanol, but proceeds only on addition of a base.

6. Detection of Centers of Asymmetry on the Basis of Magnetic Nonequivalence

Instead of optical activity, NMR spectroscopy may be used for the detection of centers of asymmetry on transition metal atoms. Because of the large contact shifts, paramagnetic complexes of the type *(7)* give well-resolved ^{1}H-NMR spectra[80,81]. If the ligands contain centers of asymmetry, the spectra show signals for all possible diastereoisomers including the various configurations on the metal atom.

It is convenient at this point to discuss more fully the detection of centers of asymmetry on transition metal atoms on the basis of magnetic nonequivalence, the principles of which are summarized below[82,83]. In compounds of the "ethane type", the protons of a methylene

group generally give only one NMR signal. The situation changes when the grouping CH_2X is attached to a center of asymmetry. In compounds of this type, the methylene protons are diastereotopic, and hence magnetically nonequivalent[82,83]. This is illustrated by the Newman projections of the three staggered conformations (Fig. 4). In I, the proton H′ is situated between the substituents a and b of the center of asymmetry, while H″ is between the substituents a and c. As in I, the environments of the two hydrogen atoms H′ and H″ are also different in the other two Newman projections II and III. The magnetic nonequivalence is not cancelled out by fast rotation about the central C—C bond. The methylene protons should therefore give different signals in the ^{1}H-NMR spectrum. Consequently, the CH_2X grouping may be used as a probe for centers of asymmetry[82,83]. This discussion is valid not only for the protons of a methylene group but also for diastereotopic *gem*-methyl groups in compounds of the type $Y—C(CH_3)_2X$ or $Y—P(CH_3)_2X$. *gem*-Methyl groups on the phosphorus can be introduced into transition metal complexes with phenyldimethylphosphane, which has already been used for the investigation of the structures of octahedral complexes with several substituents[84].

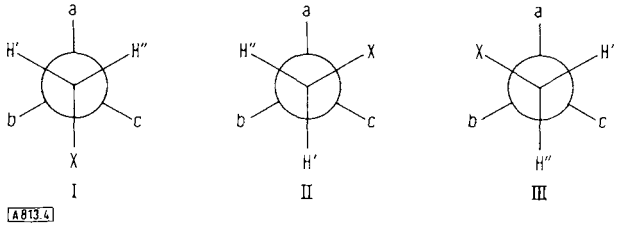
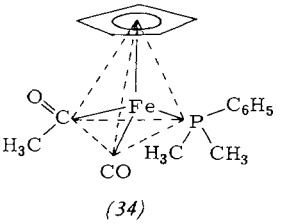


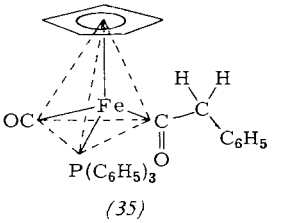
Fig. 4. Newman projections of the staggered conformations of the molecule type abcC—CH_2X.

In a reaction similar to (4), $C_5H_5Fe(CO)_2CH_3$ *(19)* and $P(CH_3)_2C_6H_5$ give the product *(34)*, a compound with a center of asymmetry on the iron atom and *gem*-methyl groups on the phosphorus[85,86]. In addition to the signals of the phenyl protons of the phosphane, the cyclopentadienyl protons (which are split by the phosphorus), and the methyl protons of the acetyl group, the ^{1}H-NMR spectrum of this complex (Fig. 5) contains four practically equidistant signals, which can be assigned to the two magnetically nonequivalent methyl groups. The signals of the two different methyl groups are split here into doublets as a result of coupling with the nuclear spin of the phosphorus. The magnetic nonequivalence of the *gem*-methyl groups confirms the presence of a center of asymmetry on the iron atom in *(34)*[85,86].

Like the methyl compound *(19)*, the corresponding benzyl compound $C_5H_5Fe(CO)_2CH_2C_6H_5$, which also contains



(34)



(35)

a probe for centers of asymmetry in the form of the grouping $CH_2C_6H_5$, can also react with triphenylphosphane[85,86]. There results the complex *(35)*, in which the methylene group is separated from the center of asymmetry

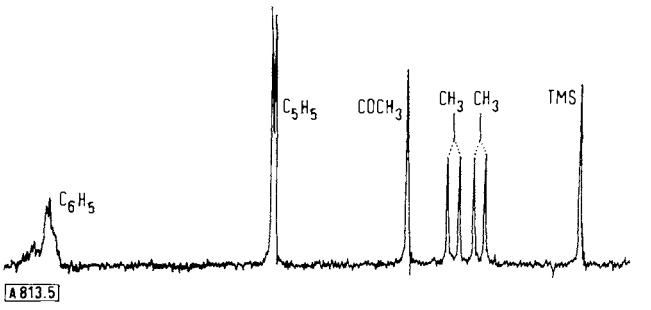
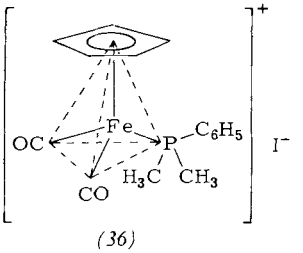
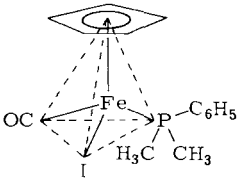


Fig. 5. ^{1}H-NMR spectrum of $C_5H_5Fe(CO)(COCH_3)P(CH_3)_2C_6H_5$ *(34)* in CS_2 solution.

on the iron atom by a CO bridge. Nevertheless, a well resolved AB system is again observed for the two magnetically nonequivalent methylene protons[85,86]. $C_5H_5Fe(CO)_2I$ *(21)* reacts with $P(CH_3)_2C_6H_5$, as shown for $P(C_6H_5)_3$ in equation (5), to give a salt *(36)* and a neutral product *(37)*[85,86]. The cation of the salt *(36)* contains two CO groups, and hence has a plane of symmetry, which leads to magnetic equivalence of the *gem*-methyl groups on the phosphorus. The ^{1}H-NMR spectrum therefore contains only one methyl signal, which is split into a doublet as a result of coupling with the phosphorus[85,86]. This example thus shows that the magnetic nonequivalence of the *gem*-methyl groups in *(34)* is due only to the asymmetric metal atom.



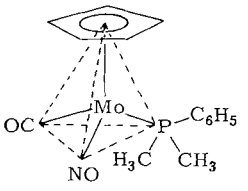
(36)



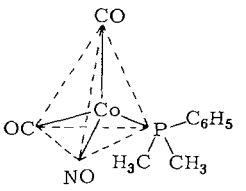
(37)

In the substitution product *(37)*, the iron atom is again surrounded by four different ligands. The magnetic nonequivalence of the two geminal methyl groups on the phosphorus demonstrates the presence of a center of asymmetry on the metal atom in *(37)*[85,86].

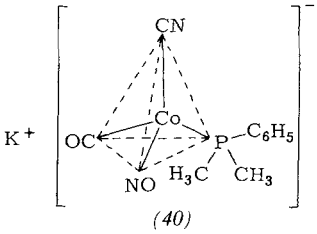
In the chiral iron complexes *(34)*, *(35)*, and *(37)*, the four different ligands differ considerably in each compound. In the complex $C_5H_5Mo(CO)(NO)P(CH_3)_2C_6H_5$ *(38)*, which can be prepared in a reaction analogous to equation (2), the carbonyl and nitrosyl ligands are extremely similar both in their linear structure and in the similar charge distribution. It was therefore interesting to consider whether the differences between the two ligands are sufficient to induce magnetic nonequivalence in the probe $P(CH_3)_2C_6H_5$. As can be seen from the ^{1}H-NMR spectrum in Figure 6, splitting is in fact present. However, it is much weaker than in *(34)*, *(35)*, and *(37)*.



(38)



(39)



(40)

The compound $Co(CO)_2(NO)P(CH_3)_2C_6H_5$ *(39)*[86] contains two CO ligands. The *gem*-methyl groups on the phosphorus are therefore magnetically equivalent, as in the complex *(36)*. In the product *(40)* of the reaction of

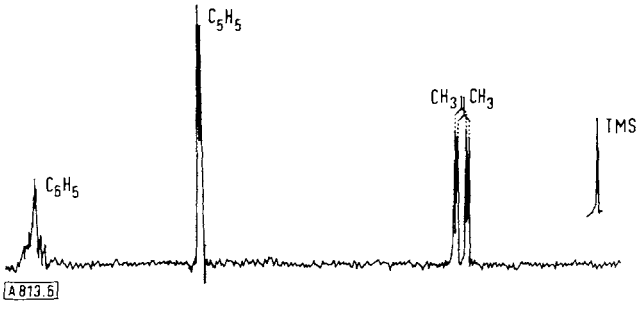


Fig. 6. ^{1}H-NMR spectrum of $C_5H_5Mo(CO)(NO)P(CH_3)_2C_6H_5$ *(38)* in CS_2 solution.

(39) with KCN [cf. equation (6)], on the other hand, the cobalt atom is surrounded by four different ligands, of which the CO, the NO, and the CN groups are very similar[86]. However, magnetic nonequivalence of the *gem*-methyl groups on the phosphorus is also found for this compound. The differences between the CO, NO, and CN ligands are thus large enough for the *gem*-methyl groups in the probe $P(CH_3)_2C_6H_5$ to show that the environment of the cobalt atom is asymmetric[86].

7. Temperature Dependence of the Nuclear Magnetic Resonance Spectra

Besides showing the presence of centers of asymmetry, the NMR spectra can also provide information about the stability of the configuration at the transition metal atom through their temperature dependence. Thus fast ligand exchange *via* symmetrical intermediates, *e.g.* in accordance with equation *(17)*, which is similar to the racemization mechanism (13), should lead to the disappearance of the magnetic nonequivalence, and hence to the coalescence of the four signals in Figures 5 and 6 to form a pair. However, this does not occur either at or above room temperature. The temperature dependence has been investigated up to 100 °C for *(34)*, up to 110 °C for *(40)*, and up to 130 °C for *(38)*[86]. The complexes decompose at higher temperatures. Up to the temperatures indicated, however, even the line broadening that should precede the coalescence of the signals cannot be observed. The complexes thus exhibit surprising configurational stability[86].

However, the temperature dependence of the NMR spectra can also be used quantitatively. If signals coalesce with rising temperature, the rate constants of the reactions involved can be found from the spectra[87]. If the coalescence temperature is not reached, as in the cases of *(34)*, *(38)*, and *(40)*, it is still possible to give upper limits for the reaction rates, in this case for the change in configuration on the metal atoms[87,88]. Upper limits found in this way for the rate constants of the ligand exchange are shown in the left-hand side of Table 1[86].

Table 1. Rate constants (in s^{-1}) of ligand exchange and epimerization reactions.

T(°C)	Ligand exchange [a]	Epimerization [b]
100	70.3 *(34)*	1.7 *(27b)*
110	15.6 *(40)*	4.6 *(27b)*
130	12.5 *(38)*	30.2 *(27b)*

[a] Upper limits determined by NMR spectroscopy [86].
[b] Extrapolated to higher temperatures from the Arrhenius diagram [73, 86].

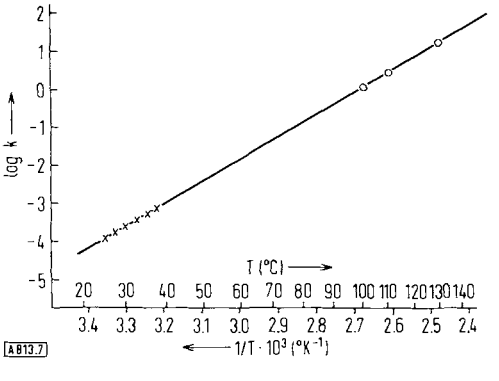
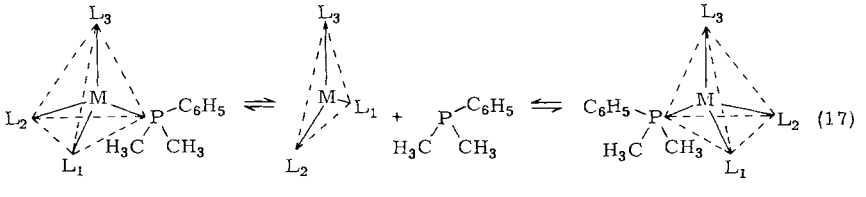


Fig. 7. Extrapolation of the Arrhenius diagram of *(27b)* to higher temperatures.

As was mentioned, the rate constants for the epimerization of the manganese compounds *(27a)* and *(27b)* have been determined in the temperature range 25–40 °C by polari-



(17)

metric kinetics[73]. Extrapolation to temperatures of 100–130°C in the Arrhenius diagram for *(27b)* (Fig. 7), assuming a constant activation energy, gives the rate constants shown in the right-hand side of Table 1[86], which cannot be measured polarimetrically, since *(27b)* decomposes thermally above 40°C[73]. These values may be compared with the upper limits of the rate constants for the ligand exchange in the complexes *(34)*, *(38)*, and *(40)* as found by NMR spectroscopy. The same process, *i.e.* the change in the configuration on the asymmetric metal atom, is measured in both methods. If it is considered that the values in the left-hand side of Table 1 give only upper limits, while the true rate constants are much smaller, it is found that the complex *(38)* and probably also *(40)* and *(34)* have greater configurational stability than the manganese derivative *(27b)*[86]. This means that the complexes *(34)*, *(38)*, and *(40)*, if they were to exist in an optically active form, would racemize more slowly than the manganese complex *(27b)*, which has already been prepared in an optically active form. This is a point that requires experimental verification.

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COMMUNICATIONS

Photochemical Synthesis of Bis(1,3-diene)monocarbonyliron Compounds

By *Ernst Koerner von Gustorf, Jürgen Buchkremer, Zorka Pfajfer*, and *Friedrich-Wilhelm Grevels*[*]

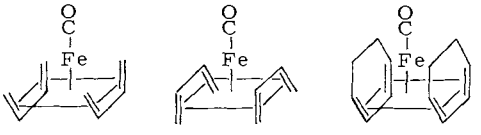
Thermal reaction of butadiene with iron carbonyls results in replacement of at most two CO ligands by butadiene[1]. Thus butadiene and $Fe(CO)_5$ react in an autoclave at 140 °C to give butadienetricarbonyliron *(1)* in 42 % yield[2].

The photochemical preparation of *(1)* at 20 °C[3,4] gives higher yields. During a study of this reaction we found that bis(butadiene)monocarbonyliron *(2)*, the first example of a new type of olefincarbonyliron complexes[5], is formed as by-product. Under appropriate conditions *(2)* becomes the main product (see experimental part). The complex crystallizes from pentane at −78 °C as orange-red tetragonal crystals of several centimeters length (m.p. 130–135 °C, decomp.). The crystals are stable in air at room temperature.

The structure of *(2)* follows from the ^{1}H-NMR spectrum, whose splitting pattern is superimposable with that[6] of *(1)*, thus establishing the symmetrical arrangement of the butadiene units. This assumption is confirmed by the space group $P\bar{4}2_1m$ found by X-ray structure analysis[5,7]. By analogy with the position of the butadiene[8] in *(1)*, the former of the two alternatives *(2a)* and *(2b)* appears the more probable.

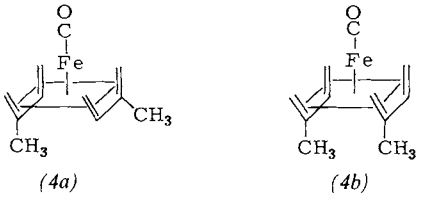
Apart from the molecular ion, the mass spectrum of *(2)* shows fragments that arise from the successive loss of CO and two butadiene units. As expected, only one CO stretching mode at 1984.5 cm^{-1} (in *n*-hexane) is seen in the IR spectrum.

Under the conditions worked out for *(2)*, $Fe(CO)_5$ reacts photochemically with 1,3-cyclohexadiene to give a 40 % yield of bis(1,3-cyclohexadiene)monocarbonyliron *(3)* that also forms orange-red crystals (m.p. 134–136 °C; decomp.; $\tilde{\nu}_{CO}$ = 1964.5 cm^{-1}). The ^{1}H-NMR spectrum again exhibits coupling constants corresponding to those observed for 1,3-cyclohexadienetricarbonyliron[9]. X-Ray structure analysis[7] confirms a symmetric arrangement of ligands and shows that the CH_2—CH_2 groups of the cyclohexadiene are turned towards the carbonyl group. This substantiates the assignment of structure *(2a)* to compound *(2)*.



(2a) *(2b)* *(3)*

Irradiation of $Fe(CO)_5$ with isoprene affords bis(isoprene)monocarbonyliron *(4)* (m.p. 99–104 °C, decomp.; $\tilde{\nu}_{CO}$ = 1980 cm^{-1}). According to the ^{1}H-NMR spectrum the two CH_3 groups in *(4)* are chemically equivalent[10]. Of the two isomers *(4a)* and *(4b)* only one is apparently present; consideration of models indicates that *(4a)* is the more likely structure as it involves less interaction between the two isoprene units.



(4a) *(4b)*

The diene-iron bond, *e.g.* in *(2)*, can be cleaved again photochemically; in the presence of 1,3-cyclohexadiene compound *(3)* is formed as a result of ligand exchange.

The bis(diene)monocarbonyliron compounds are isosteric with the starting materials – such as, for example, bis(1,5-cyclooctadiene)nickel(0) – for the preparation of nickel catalysts used in the oligomerization of butadiene[11]. On coordination with CO iron becomes formally isoelectronic with nickel(0); bis(diene)monocarbonyliron complexes therefore also catalyze the oligomerization of butadiene. In the presence of n-donors such as phosphanes butadiene can be dimerized to 4-vinyl-1-cyclohexene and 1,5-cyclooctadiene by catalytic amounts of *e.g. (2)* or *(3)* at temperatures of about 100 °C. When no phosphane is present, trimerization to 1,5,9-cyclododecatriene and other butadiene trimers is observed[12]. The bis(diene) complexes of other transition metals of corresponding structure and electronic configuration should also fulfill the requirements for catalytic activity.

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Procedure for the preparation of (2):

$Fe(CO)_5$ (0.05 mole) and butadiene (1 mole) in pentane (300 ml) are irradiated at −35 °C under argon for 48 h in an immersion-lamp apparatus with internal and external cooling using a high pressure mercury arc lamp, Philips HPK 125 W. The coolant is first passed through the external cooling mantle and then through the internal one. The temperature gradient causes the product *(2)* to crystallize at the outer wall of the reaction vessel. After irradiation, the solution is allowed to warm to room temperature whereupon *(2)* dissolves and can be freed from small amounts of brown decomposition products by inverse filtration. On renewed cooling of the filtrate to −78 °C, crystalline *(2)* of analytical purity is precipitated in 85–90 % yield (based on $Fe(CO)_5$).

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[5] *R. E. Davis, G. L. Cupper*, and *H. D. Simpson*, Amer. Crystallogr. Assoc. Summer Meeting, August 1970, Ottawa, Abstr. N 4, mention an X-ray structure analysis of *(2)*, which has apparently also been prepared at the University of Texas, Austin (USA). *Note added in proof:* Meanwhile *(2)* has also been prepared by reaction of butadiene with ferric chloride in ether at −78 °C in the presence of isopropylmagnesium chloride and saturation of the reaction mixture with carbon monoxide. Apparently this process is suitable only for the preparation of small amounts of the complex; the yield is about 30% [*A. Carbonaro* and *A. Greco*, J. Organometal. Chem. *25*, 477 (1970)].

[6] The ^{1}H-NMR spectra of *(1)* and *(2)* in C_6D_6 show multiplets at $\tau = 5.25$ (2H), 8.6 (2H), and 10.06 (2H), and at $\tau = 5.73$ (2H), 9.0 (2H), and 10.35 (2H), respectively. — *M. L. Maddox, S. L. Stafford*, and *H. D. Kaesz*, Advan. Organometal. Chem. *3*, 1 (1965), give an analysis of the coupling constants for *(1)*.

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[9] The ^{1}H-NMR spectra of 1,3-cyclohexadienetricarbonyliron and *(3)* in C_6D_6 show multiplets at $\tau = 5.3$ (2H), 7.2 (2H), and 8.6 (4H), and at $\tau = 5.66$ (2H), 7.46 (2H), 8.05 (2H), and 8.95 (2H), respectively. — *R. Burton, L. Pratt*, and *G. Wilkinson*, J. Chem. Soc. *1961*, 594, give an analysis of the coupling constants of the tricarbonyl complex.

[10] The ^{1}H-NMR spectra of isoprenetricarbonyliron and *(4)* in C_6D_6 show multiplets (m) and singlets (s) at $\tau = 5.1$ (1H; m), 8.17 (3H; s), 8.53 (2H; m), and 10.1 (2H; m), and at $\tau = 6.1$ (1H; m), 8.32 (3H; s), 8.93 (2H; m), and 10.4 (2H; m) respectively.

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[12] A detailed discussion will appear elsewhere.

Molecular and Crystal Structure of Bis(1,3-cyclohexadiene)monocarbonyliron

By *Carl Krüger* and *Yi-Hung Tsay*[*]

Bis(1,3-cyclohexadiene)monocarbonyliron *(1)*[1], a compound of interest because it is isosteric with starting materials employed in the production of highly active nickel catalysts, crystallizes in the orthorhombic space group $P2_12_12_1$ along {001} with the following cell constants: $a = 17.089 \pm 0.0005$, $b = 8.495 \pm 0.0004$, $c = 7.545 \pm 0.0004$ Å; $Z = 4$; $d(\text{calc}) = 1.48$ g cm^{-3}.

The molecular structure was deduced by the heavy atom method from 1697 diffractometer data and, including the unequivocally located hydrogen atoms, refined anisotropically to an R factor of 3.3%.

Unlike bis(1,3-butadiene)monocarbonyliron[2] ($a = 7.76$, $c = 7.33$ Å), whose space group $P\bar{4}2_1m$ requires the molecule to have C_s symmetry, complex *(1)* is chiral and has only approximately m-symmetry. In spite of their fairly close contact to the carbonyl group, the C_6 rings are arranged as shown in Fig. 1; Fig. 2 shows a view along the Fe—CO axis.

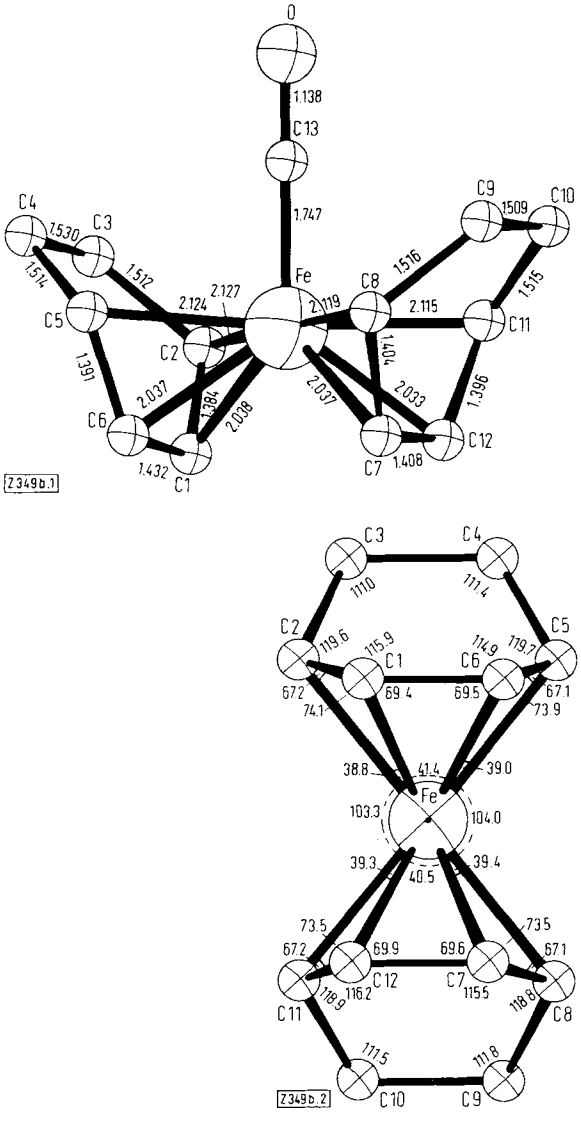
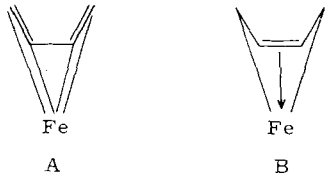


Fig. 1 (above) and 2 (below). Maximum estimated errors: lengths ±0.006 Å; angles ±0.5°.

The two rings differ in conformation and in their bonding to the iron by amounts that are too large to be accounted for by experimental errors. This may be due to slight predominance of the limiting structure A in ring 1 (C1–C6), and structure B in ring 2 (C7–C12). Both kinds of bonding have been considered for analogous diene complexes[3]. However, the observed distortions could only be induced

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by the asymmetry of the crystal field. The central atom lies 0.1 Å above the best plane through the atoms C2, C5 and C8, C11. The lines joining the atoms C2–C5 and C8–C11 respectively are twisted through 1°.



A B

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[1] *E. Koerner von Gustorf, J. Buchkremer, Z. Pfajfer,* and *F.-W. Grevels,* Angew. Chem. *83*, 249 (1971); Angew. Chem. internat. Edit. *10*, 260 (1971).

[2] See also: *R.E. Davis, G.L. Cupper,* and *H.D. Simpson,* Amer. Crystallogr. Assoc. Summer Meeting, August 1970 Ottawa, Abstr. N4.

[3] *O. S. Mills* and *G. Robinson,* Acta Crystallogr. *16*, 758 (1963); *M. R. Churchill* and *R. Mason,* Proc. Roy. Soc. (London) *A 301*, 433 (1967); *R. Eiss,* Inorg. Chem. *9*, 1650 (1970).

Concerning the Existence of 1-Norbornene

By *Reinhart Keese* and *Ernst-Peter Krebs*[*]

Bredt's rule categorically denies the possibility of a normal double bond at the bridgehead of the norbornane system[1]. However, it remains an open question whether bicyclo-[2.2.1]hept-1-ene *(8)* with its highly strained double bond[2] can be detected[3], possibly as a metastable intermediate.

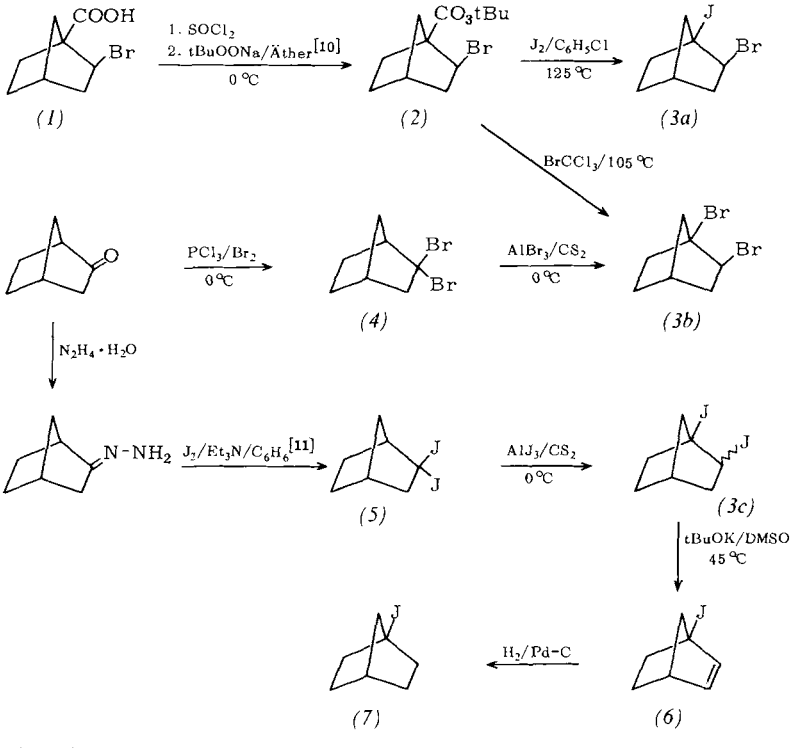
In the present communication we report the results of bis-dehalogenation of 1,2-dihalogenonorbornanes. The starting materials *(3a)–(3b)* were prepared as shown in Scheme 1[4].

Fragmentation of *(2)*[6a] in cumene at 130 °C gives 2-*exo*-bromonorbornane[7]; this supports both the *exo*- configuration of *(1)*[8] and that of *(3a)* [NMR: 4.15 (o, $J = 7.5$, 3.5, 1.5; 1 H), 2.8–0.7 (*ca.* 9 H); mass spectrum: 302/300 (M^+), 221 (M^+–Br)][9]. The constitution and configuration of *(3b)*[6b] are apparent from its formation on thermolysis of *(2)* in bromotrichloromethane [NMR: 4.15 (o, $J = 7.0$, 3.5, 1.8; 1 H), 2.7–1.0 (*ca.* 9 H); mass spectrum: 256/254/252 (M^+), 175/173 (M^+–Br)].

The constitution of *(3c)* [NMR: 4.30 (o, $J = 8.0$, 4.0, 1.5; 1 H), 2.8–1.0 (*ca.* 9 H); mass spectrum: 348 (M^+), 221 ($M^+ - I$)], which is formed almost quantitatively from *(5)*, is supported by *(7)*—obtained *via (6)* [NMR: 6.18 (d, $J =$ 5.5; 1 H), 5.88 (q, $J = 5.5$, 3.0; 1 H), 2.7–1.0 (7 H); mass spectrum 220 (M^+), 192 ($M^+ - C_2H_4$)]—whose IR spectrum is identical with that of 1-iodonorbornane[12] prepared by conventional means; the probable[13] *exo* configuration of *(3c)* remains to be confirmed.

The elimination of halogen from *(3a)*, which is induced by *n*-butyllithium and proceeds *via* lithium-iodine exchange[14], gives, in the presence of furan, the isomeric adducts *(9a)* and *(9b)*. Three saturated hydrocarbons of composition $C_{14}H_{20}$ whose structures are unknown were isolated as by-products (see Scheme 2 and Table).

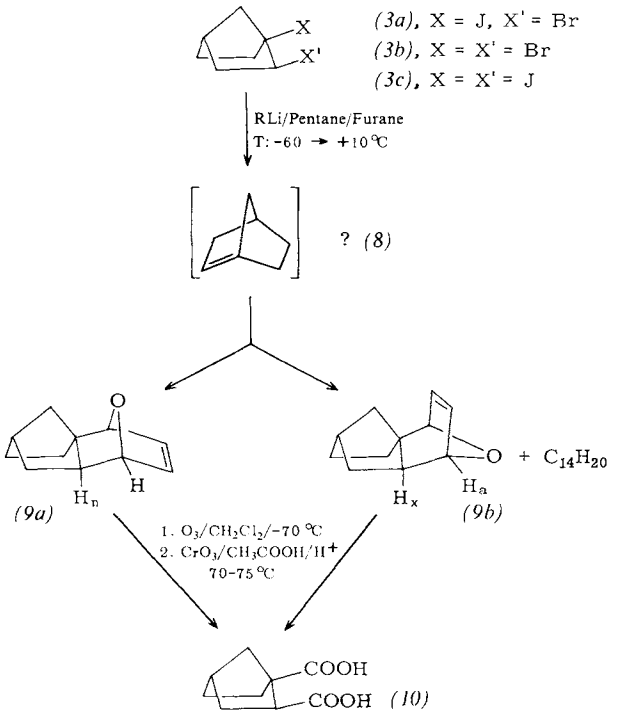
The furan adducts *(9a)* and *(9b)* differ significantly in their NMR coupling constants. In *(9b)* H_x is *exo* to H_a ($J_{ax} = 4.0$ Hz), whereas H_n in *(9a)* is *endo* to the proton at the ether bridge and consequently is not coupled with it[15].



Scheme 1.

Ozonolysis and subsequent chromic acid oxidation of both isomers *(9a)* and *(9b)* affords the same 1,2-*exo*-norbornanedicarboxylic acid *(10)*[16]. The constitution

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Scheme 2.

Cpd.	R—Li R	Furan adducts (9a)+(9b) yield (%)	(9a):(9b) [a]	Hydrocarbons $C_{14}H_{20}$ yield	ratio [b]
(3a)	*n*-Butyl	55	23:77	18	37:12:51
	n-Butyl [c]	56.5	22:78	40	44:14:42
	sec-Butyl	18	25:75	63	49:14:37
	n-Butyl	— [d]		74	52:15:33
(3b)	*sec*-Butyl	16	22:78	— [e]	
(3c)	*n*-Butyl [f]	62	20:80	19	53:10:37
	sec-Butyl	28	23:77	37	58:11:31

[a] Gas chromatography area ratios.
[b] Arranged in the order of increasing GLC retention times; area ratios.
[c] After 84% conversion.
[d] In diethyl ether.
[e] Mixture, not identified.
[f] After 52% conversion.

of this acid is confirmed by independent synthesis starting from the Diels-Alder reaction between methyl cyclopentadienecarboxylate[17] and allyl acetate.

All the trapping reactions so far carried out with furan give the same ratio of the adducts *(9a)* and *(9b)* (see Table). We regard this result as compelling evidence for the intermediacy of bicyclo[2.2.1.]hept-1(2)-ene *(8)*.

The question whether the highly reactive intermediate *(8)* is susceptible to detection at all and whether it is a triplet or a singlet molecule warrants further study. Experiments to detect bicyclo[2.2.1.]hept-1(7)-ene are also currently in progress.

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[1] *J. Bredt*, Liebigs Ann. Chem. *437*, 1 (1924).

[2] *Bredt's* rule in the sense in which it is usually understood nowadays.

[3] a) See, *e.g.*, the following studies on larger bicycloalkane systems: *P.D. Bartlett* and *L.H. Knox*, J. Amer. Chem. Soc. *61*, 3184 (1939); *V. Prelog*, *P. Barmann*, and *M. Zimmermann*, Helv. Chim. Acta *32*, 1284 (1949); *J.A. Marshall* and *H. Faubl*, J. Amer. Chem. Soc. *92*, 948 (1970); *J.R. Wiseman* and *W.A. Pletcher*, *ibid.* *92*, 962 (1970); b) *J.A. Berson* and *M.R. Willcott*, J. Org. Chem. *30*, 3569 (1965). A consideration of the enthalpy of the transition state and of the pre-exponential term led to the conclusion that: "anti-Bredt species [*e.g. (8)*] would be kinetically inaccessible by way of conventional olefin-forming reactions."

[4] The new compounds are racemic, pure according to GLC and/or NMR spectra, and gave correct elemental analyses; the NMR [δ(ppm), TMS internal standard, *J*(Hz); $CDCl_3$ or CCl_4 as solvent] [5], mass (*m/e*), and IR spectra support the structures given; b) a detailed description of the experiments mentioned in this communication is planned.

[5] We are grateful to Prof. *W. v. Philipsborn*, Universität Zürich, for recording some of the NMR spectra.

[6] In collaboration with a) *P. Bützer* (Diplomarbeit ETH, 1970) and b) *J. Frank* (Diplomarbeit ETH, 1969).

[7] *J.D. Roberts*, *E.R. Trumbull*, *W. Bennet*, and *R. Armstrong*, J. Amer. Chem. Soc. *72*, 3116 (1950).

[8] *W.R. Boehme*, J. Amer. Chem. Soc. *81*, 2762 (1959); *H. Kwart* and *G. Null*, *ibid.* *81*, 2765 (1959).

[9] *(3a)* is formed directly from *(1)* on photolysis in a benzene solution of *tert*-butyl hypoiodite (*E.-P. Krebs*, Diplomarbeit ETH, 1968); cf. *D.H.R. Barton*, *H.P. Faro*, *E.P. Serebryakov*, and *N.F. Woolsey*, J. Chem. Soc. *1965*, 2438.

[10] *P.D. Bartlett* and *J.M. McBride*, J. Amer. Chem. Soc. *87*, 1727 (1965).

[11] *D.H.R. Barton*, *R.E. O'Brien*, and *S. Sternhell*, J. Chem. Soc. *1962*, 270. In those cases of iodination of keto hydrazones by this method that have come to our knowledge no geminal diiodo products were obtained.

[12] *P.T. Lansbury*, *V.A. Pattison*, *J.D. Sidler*, and *J.B. Bieber*, J. Amer. Chem. Soc. *88*, 78 (1966).

[13] a) Compare the isomerization of *(4)* and that of 2,2-dichloronorbornane, which lead predominantly to *(3b)* and 1,2-*exo*-dichloronorbornane respectively [13b]; b) *A.J. Fry* and *W.B. Farnham*, J. Org. Chem. *34*, 2314 (1969).

[14] In an elimination experiment, 73% (area of GLC signal) of *n*-butyl iodide was detected; the *n*-butyl iodide isolated was identified by comparison of IR spectra [6a].

[15] Cf. *P. Laszlo* and *P.v.R. Schleyer*, J. Amer. Chem. Soc. *86*, 1171 (1964).

[16] Melting point, mixed melting point, and IR spectrum.

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A New Route to Derivatives of Bicyclo[2.1.1]hexene and Tricyclo[3.1.0.0^{2,6}]hexane

By *Wolfgang Kirmse* and *Friedrich Scheidt*[*]

In conjunction with our work on bicycloalkyldiazonium ions[1] we have studied the decomposition of *N*-nitroso-*N*-*exo*-bicyclo[3.1.0]hex-2-en-6-ylurea *(1)*. Compound *(1)* was prepared, analogously to the saturated compound[1], from cyclopentadiene and ethyl diazoacetate. Alkaline cleavage of *(1)* with 2 mol. equiv. of sodium carbonate as base gave benzene as the sole product. Benzene is the product expected from deprotonation of the cyclohexadienyl cation *(5)* formed by a cyclopropyl-allyl rearrangement. However, the *exo*-diazonium ion *(2)* cannot be transformed into *(5)* in a concerted process (outward disrotation). We therefore assume that benzene formation is preceded by a base-catalyzed isomerization of the *exo*-diazonium ion *(2)* to the *endo* species *(3)*. This assumption is confirmed by the incorporation of deuterium in deuterated solvents.

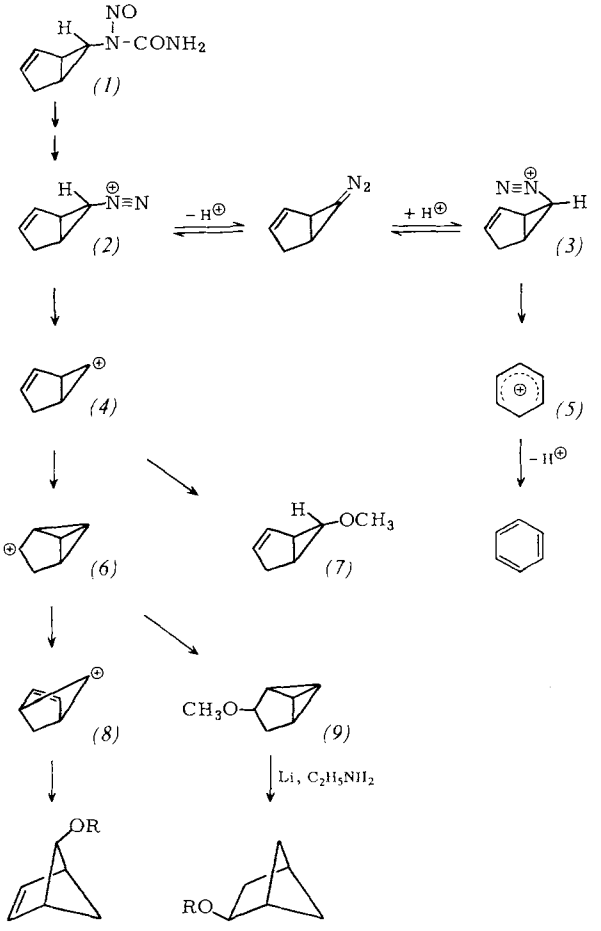
Under less strongly alkaline conditions, benzene is accompanied by substitution products (Table). In methanol the reaction yields *exo*-6-methoxybicyclo[3.1.0]hex-2-

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ene *(7)* (identified by comparison with a product formed from methoxycarbenoid and cyclopentadiene[2]) and methoxytricyclo[3.1.0.0^{2,6}]hexane *(9)*. The structure of *(9)* is established by spectroscopic data [NMR: 60 MHz, ppm relative to TMS: 3.87 (1H/dd); 3.13 (3H/s); 2.45 (2H/m); 2.32 (1H/m); 2.1 (1H/m); 1.75 (2H/m)] and by the cleavage of the C-2—C-6 bond by lithium in ethylamine[3] to give 2-methoxybicyclo[2.1.1]hexane *(13)*. Compound *(13)* was prepared for comparison from the known compound bicyclo[2.1.1]hexan-2-ol[4].

Table. Reactions of *(1)*.

Solvent	Base (mol. equiv.)	T(°C)	Products (yield)
Methanol	none	40	*(7)* (23%)
	NaOCHO (2)	20	*(7)* (2–3%) *(9)* (35%) benzene (43%)
	$NaHCO_3$ (2)	20	*(9)* (18%) benzene (72%)
	Na_2CO_3 (2)	20	benzene (90%)
Water/dioxane (10:8)	NaOCHO (1.2)	20	*(11)* (20%) benzene (7%)
	$NaHCO_3$ (1.2)	0	*(10)* (14%) benzene (5%)
	$NaHCO_3$ (1.2)	20	benzene (55%)
Water/THF (1:1)	NaOCHO (1.3)	20	*(10)* (5%) *(11)* (23%) benzene (14%)



Reaction in water/dioxane gave *anti*-bicyclo[3.1.1]hex-2-en-5-ol *(10)* and, on use of sodium formate as base, the corresponding formic ester *(11)*. *anti*-5-Acetoxybicyclo[2.1.1]hex-2-ene *(12)* was obtained by deamination of *exo*-bicyclo[3.1.0]hex-2-en-6-ylammonium chloride in glacial acetic acid/sodium acetate at pH 4.7 in 24% yield. The spectral data of *(10)*–*(12)* agree with those given for *(12)* in the literature[5].

The transition *(2)*→*(9)* is a homoallyl-cyclopropylcarbinyl rearrangement and the conversion *(2)*→*(10)* is a homoallyl-homoallyl rearrangement. The cationic intermediates [*(4)*, *(6)*, and *(8)*] – formulated as classical ions in the reaction scheme – are probably bridged systems. This is suggested by the stereospecific formation of *exo*-*(7)* and *anti*-*(10)*. The rearrangement leads to products exhibiting greater strain than the starting materials: bicyclo[2.1.1]hexenes undergo thermal rearrangement to bicyclo[3.1.0]hexenes[5–7].

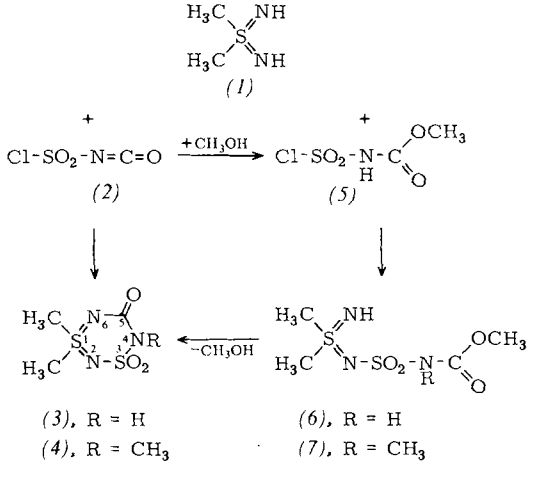
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Preparation of 1,1-Dimethyl-5-oxo-4,5-dihydro-1,3,2,4,6-thia(VI)thiatriazine 3,3-Dioxide from Dimethyl Sulfone Diimine[1]

By *Manfred Haake*[*]

The novel heterocyclic compound 1,1-dimethyl-5-oxo-4,5-dihydro-1,3,2,4,6-thia(VI)thiatriazine 3,3-dioxide *(3)* has now been isolated after repeated purification from the products of the reaction between chlorosulfonyl isocyanate



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(2) and dimethyl sulfone diimine *(1)*[1,2] in the presence of triethylamine.

Preparation of *(3)* by a modified route proved to be more favorable. Thus compound *(1)*, to which triethylamine has already been added, is first condensed with *N*-chlorosulfonylurethane *(5)* (which is readily accessible from *(2)* and methanol[3] and which forms reactive intermediates with triethylamine[4]) to give methoxycarbonylsulfamoyl dimethyl sulfone diimine *(6)* (yield 80%). Brief heating of *(6)* in boiling DMF affords *(3)* in almost quantitative yield.

Compounds *(3)* and *(6)* are readily soluble in water and, because they contain the SO_2—NH—CO group, they can be titrated as monobasic acids[3]. Their acid character is also demonstrated by reaction of *(3)* and *(6)* with diazomethane to give the *N*-methyl compounds *(4)* and *(7)*.

The structures of *(3)*, *(4)*, *(6)*, and *(7)* were confirmed by elemental analysis, molecular weight determinations (mass spectra), and IR and NMR spectrometric measurements (see Table).

	M.p. (°C)	IR: ν(cm^{-1}) NH	CO	NMR: δ(ppm) in [D$_6$]DMSO SO_2NH	SNH	$S(CH_3)$	OCH_3	NCH_3
(3)	182 (dec.)	3240	1667	11.2	—	3.70	—	—
(4)	190 (dec.)	—	1656	—	—	3.75	—	3.13
(6)	172 (dec.)	3320	1754	7	7	3.38	3.67	—
		3010	1742					
(7)	83	3290	1740	-	4.0	3.35	3.70	3.10

Attempts to convert the ester *(7)* into *(4)* by boiling in DMF were unsuccessful. This would suggest[5] that the facile condensation of *(6)* to form the compound *(3)* proceeds *via* an elimination-addition mechanism involving a sulfonyl isocyanate intermediate.

Procedure:

A solution of *(5)* (3.76 g) in dry methylene chloride (20 ml) was added dropwise to a vigorously stirred solution of *(1)* (2.0 g) and triethylamine (2.2 g) in dry methylene chloride (20 ml) within 30 min. After an additional 30 minutes' stirring, the precipitate was filtered off and washed thoroughly with methanol; yield 3.9 g (80%) of *(6)* (can be recrystallized from acetonitrile). A solution of *(6)* (0.75 g) in dry DMF (5 ml) was heated to boiling within 3 min under a current of dry N_2. The reaction mixture was then diluted with anhydrous ethanol (50 ml) and subsequently cooled in an ice bath for several hours. The crystals were filtered off under suction and washed with a little ethanol; yield 0.6 g (93%) of *(3)* (can be recrystallized from water/isopropanol).

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N-Fluorosulfonyldichloroamine[1]

By *Herbert W. Roesky*[*]

Perfluorinated inorganic derivatives of dichloroamine are little known or unstable[2,3]. *N*-Fluorosulfonyl sulfur oxide imide reacts with chlorine monofluoride at room temperature with cleavage of thionyl fluoride to give *N*-fluorosulfonyldichloroamine *(1)* in high yield.

$$FSO_2N{=}S{=}O + 2ClF \rightarrow \underset{(1)}{FSO_2NCl_2} + SOF_2$$

(1) is a pale yellow liquid which can be distilled undecomposed at reduced pressure: b.p. 29—30°C/75 torr. On standing the compound slowly decomposes with formation of Cl_2, N_2, and FSO_2Cl. Its identification followed from elemental analysis and the mass spectrum: *m/e* 171, 169, 167 (molecular ion); 134, 132 (FSO_2NCl); 88, 86, 84 (NCl_2); 83 (SO_2F) and smaller fragments. The molecular weight was determined by cryoscopic measurements (in benzene) to be 165.

The IR spectrum (capillary film between AgCl plates) shows absorptions at (cm^{-1}): 1458 vs, 1222 vs, 1025 w, 844 vs, 790 vs, 630 m, 588 vs, 522 m, 482 m, 440 s. They are tentatively assigned to the following vibrations: ν_{as}(SO) 1458, ν_s(SO) 1222, ν(SF) 844, ν(SN) and ν(NCl) 790, 630, and 588 cm^{-1}. The ^{19}F-NMR spectrum contains a singlet at $\delta_F = -26.5$ ($CFCl_3$ as external standard). According to IR, NMR, and mass spectra the isomeric form $ClSO_2NClF$ is less probable. Compound *(1)* liberates iodine from aqueous potassium iodide solution, the first step of the hydrolysis being formation of hypochlorous acid:

$$FSO_2NCl_2 + HOH \rightarrow \underset{(2)}{FSO_2NClH} + HOCl$$

N-Fluorosulfonylmonochloroamine *(2)* could be isolated in the form of its amide by treatment with tetraphenylphosphonium or tetraphenylarsonium chloride:

$[(C_6H_5)_4P]^+ [FSO_2NCl]^-$; m.p. 200°C (dec.)
$[(C_6H_5)_4As]^+ [FSO_2NCl]^-$; m.p. 154°C (dec.)

Both salts are colorless and are soluble in acetone and methanol.

Experimental:

FSO_2NSO (0.1 mole) is placed in a 100 ml two-necked quartz flask fitted with a delivery tube, refluxing condenser, and T-piece for purging with dry nitrogen. ClF (0.25 mole) is fed into the flask, the internal temperature of which is not allowed to increase beyond 30°C. Finally, the flask is purged with nitrogen and the liquid phase is fractionally distilled twice at 75 torr. Yield of *(1)*: 13.5 g (81%). The highest boiling fraction contained, in addition to FSO_2NSO and *(1)*, a compound which according to the ^{19}F-NMR spectrum ($J_{F-F} = 13$ Hz) could be $FSO_2NS(O)ClF$, but it could not be isolated in pure form.

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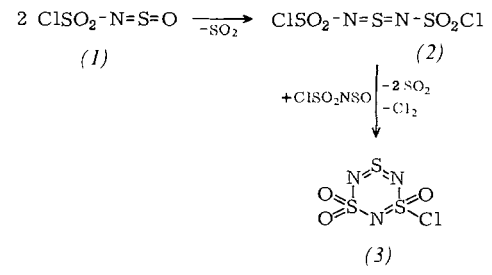
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3-Chloro-1,3,5,2,4,6-thiadithia(IV)triazine 1,1,3-Trioxide[1]

By *Herbert W. Roesky*[*]

N-Fluorosulfonyl sulfur oxide imide, $FSO_2N{=}S{=}O$, reacts with boron trichloride in methylene chloride with replacement of fluorine by chlorine. *N*-Chlorosulfonyl sulfur oxide imide[2] *(1)* loses sulfur dioxide even at room temperature. The resulting bis(*N*-chlorosulfonylimido)-sulfur *(2)* cannot be isolated by distillation: after distilling off unreacted *(1)* there remains a solid, sublimable, yellow residue. The reaction can be formulated as follows:



SO_2 could be detected by IR and mass spectrometry. The structure of the reaction product *(3)* was deduced from the results of elemental analysis, molecular weight determinations, and from the IR and mass spectra. *(3)*, m.p. 105—108 °C, is soluble in benzene and acetonitrile and is readily hydrolyzed in the presence of traces of moisture.

The mass spectrum of the sulfur-nitrogen ring *(3)* shows, alongside the molecular ion at *m/e* 223 and 221, fragment ions at *m/e* 186 ($S_3N_3O_3$), 143 (NSOClSN), 110 (SO_2NS), 83 (SOCl), 80 (SO_2NH_2), 78 (SO_2N), 64 (SO_2), 63 (SONH), 62 (SON), 48 (SO), 46 (NS). The molecular weight was determined cryoscopically in benzene to be 236 and 240.

IR spectrum (NaCl and KBr region): 1350 (vs), 1175 (vs), 1125 (vs), 1078 (s), 1025 (m), 800 (s), 662 (m), 632 (s), 571 (s), 482 (w), 468 (w) cm^{-1}. The vibrations between 1000 and 1200 cm^{-1} are tentatively assigned to $\nu_s(SO)$, $\nu(SO)$, and $\nu(S{-}N)$, and the vibration at 1350 cm^{-1} to $\nu_{as}(SO)$.

Experimental:

A powerful stream of BCl_3 is passed through a solution of FSO_2NSO (1 mole) in methylene chloride (500 ml). The temperature of the reaction mixture increases to about 35 °C. After completion of reaction the solvent is removed by evaporation and the residue is purified by distillation under reduced pressure (oil pump): Compound *(1)* b.p. 40—42 °C/1.2 torr[2]; a small amount of *(3)* (2 g) is obtained as side product.

Exposure of *(1)* (0.5 mole) to daylight for 3 weeks, or irradiation under UV light[3] in a quartz flask for 12 h leads to evolution of SO_2. Compound *(3)* can be isolated from the liquid reaction product by distillation-sublimation (oil-pump vacuum), the bath temperature of the distillation-sublimation apparatus, however, should not be allowed to increase beyond 80 °C. The compound was purified by double sublimation at 60—70 °C/0.01 torr and finally separated from small amounts of insoluble decomposition products by dissolution in benzene. Yield: 5 g.

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The Structure of Polymeric 2,4-Hexadiynylene-bis(phenylurethane)[1][***]

By *Erich Hädicke, E. C. Mez*, and *C. H. Krauch* and *Gerhard Wegner* and *Johannes Kaiser*[*]

Not only low molecular[2, 3] but also polymeric materials[4, 5] can be prepared structure-specifically and stereoselectively by topochemical reactions without using catalysts and by merely utilizing the packing properties of organic materials. For example, crystals of suitably substituted monomeric diacetylenes are converted into macroscopic polymer crystals by heat or by high-energy radiation[6]. On the basis of crystallographic and general crystallochemical considerations it had been predicted that the main chain of these polymers must be a completely conjugated system[6]. This prediction has now been confirmed by the X-ray structural analysis of the polymeric 2,4-hexadiynylenebis(phenylurethane).

For the three-dimensional X-ray structural analysis we used triclinic needles of the monomer which had been crystallized from dioxane/water, polymerized by UV irradiation ($\lambda > 240$ nm), and separated from unchanged monomer by extraction with dioxane[6]. Crystallographic data of the polymer: $a = 4.89_1$, $b = 12.53_4$, $c = 16.77_5$ Å; $\alpha = 69.3_8$, $\beta = 96.8_1$, $\gamma = 96.2_0°$; $d_{exp} = 1.37$ g cm^{-3}; space group $P\bar{1}$. The asymmetric unit contains one molecule $C_{20}H_{16}N_2O_4$ and $\frac{1}{2}$ molecule $C_4H_8O_2$ (dioxane) at the center of symmetry ($d_{calc} = 1.37$ g cm^{-3}). All reflections up to $\vartheta = 51°$ ($\vartheta/2\vartheta$ scan; 5 value measurements) were measured on a single crystal diffractometer with $Cu_{K\alpha}$ radiation. Of the 2035 reflections, only 86 were not observed ($J < 2\sigma$). 281 signs were determined from the 400 strongest reflections by triple product methods[7]. An E-Fourier synthesis using these values gave the positions of all 29 atoms ($R = 29.6\%$). Refinement by the method of least squares (full matrix) required overlapping cycles because of the large number of parameters. Isotropic refinement yielded an R factor of 12.6%. The anisotropic refinement converged to an R factor of 7.9%. We have found the majority of the expected hydrogen atoms in a difference Fourier synthesis.

Figure 1 shows the structure of a fundamental unit of the polymer chain. Comparison of this structure with the structures of the similarly polymerizable 2,4-hexadiynediacid[8] and 2,4-hexadiynediol[9] provides supporting evidence for the mechanism of polymerization suggested in previous publications[6]. As expected, the polymer chain is formed by 1,4-polymerization of the conjugated triple

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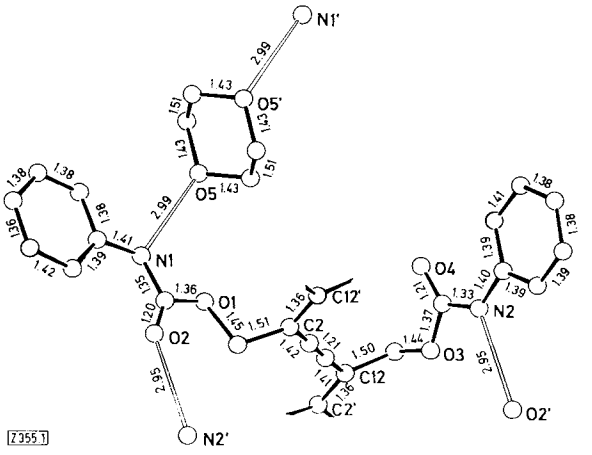
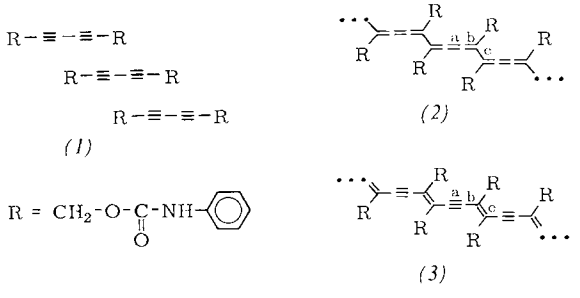


Fig. 1. Polymeric 2,4-hexadiynylenebis(phenylurethane) with hydrogen bonds to neighboring molecules and to 1,4-dioxane. Projection onto the $(1\bar{1}0)$-plane. The primed atomic positions are generated by symmetry relationships.

bonds. Previously, it has been assumed that the polymer *(2)* is formed from monomer having the skeletal structure *(1)*. The bond lengths calculated from our observations, however, are more compatible with the polymer structure *(3)* (Table 1).

Table 1. Comparison of observed and expected bond length for the polymer structures *(2)* and *(3)* [11].

	Bond lengths Å		
	a	b	c
Model *(2)*	1.28	1.32	1.46
Model *(3)*	1.21	1.43	1.34
Found	1.21	1.41	1.36



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The X-ray crystallographic findings show that the main chain of the polymer is a planar conjugated system to which the plane of the two phenylurethane side-chains are inclined at angles of 73 and 89°. The position of the phenylurethane groups is determined by hydrogen bridges to neighboring molecules and to the dioxane. Since solvent-free modifications of the monomer do not polymerize[10], it appears that the dioxane is partly responsible for the suitable packing of the molecules of monomer.

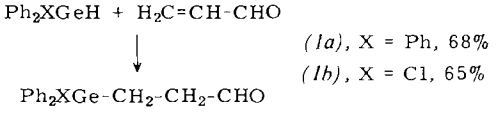
The hydrogen bonds fix the side chains and bring the conjugated triple bonds in the monomer into a suitable position for the polymerization, such that solid-state polymerization can proceed without essential change of the crystal lattice and a polymer with all-*trans* structure is formed.

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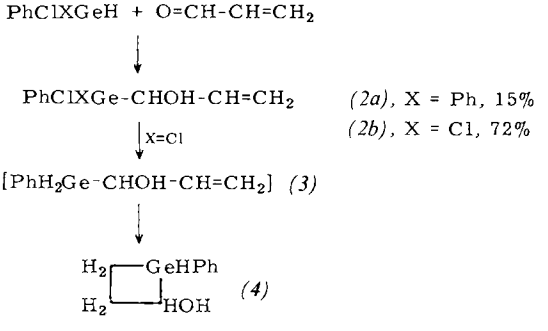
1-Germylallyl Alcohols and Germacycloalkanols

By *Pierre Rivière* and *Jacques Satgé*[*]

Substituted germanes can undergo addition to the C=C or the C=O double bonds of compounds such as acrolein. On radical initiation (UV or azoisobutyronitrile), triphenylgermane and diphenylchlorogermane add to the C=C double bond of acrolein to give 3-germylpropionaldehydes *(1a)* and *(1b)*, respectively. These reactions are inhibited by galvinoxyl and do not take place in nitromethane. In this polar solvent, the slightly positive character of the proton attached to germanium in Ph_2ClGeH is increased to such an extent that 1,2-dipolar addition to the carbonyl group to form the 1-germylallyl alcohol *(2a)* occurs in the presence of H_2PtCl_6. Under the same conditions, phenyldichlorogermane gives the 1-germylallyl alcohol *(2b)*. The clear polarization of the $\overset{\delta-}{Ge}—\overset{\delta+}{H}$ bond induced in $PhCl_2GeH$ by the combined electron-withdrawing effects of the chlorine atoms and the phenyl group favors the probably concerted dipolar addition mechanism.



The desired alcohol *(3)* could not be isolated after reduction of *(2b)* with $LiAlH_4$ at high dilution. However, in addition to polymeric products, we observed a small



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quantity of 1-phenyl-1-germa-2-cyclobutanol *(4)* formed from *(3)* by intramolecular addition (see Table).

Phenyldichlorogermane reacts on heating with crotonaldehyde to give the monoadduct *(5)* and the diadduct *(6)*. In contrast to the reaction with 1-vinyl ketones, we observed no 1,4-addition[1]. In nitromethane and in the presence of H_2PtCl_6, 1,2-dipolar addition to the carbonyl group with formation of *(5)* is strongly favored (95 % yield) since the solvent inhibits the secondary radical reaction leading to *(6)*. The diadduct *(6)* can be isolated in high yield, however, if the reaction is carried out under free-radical conditions (UV irradiation).

On heating, *(6)* decomposes in the same way as analogous 1-chloro-germyl alcohols[2]. The alcohol *(5)* decomposes similarly at 80 °C. Phenylchlorogermylene (PhGeCl) was detected by interception with dimethylbutadiene[3,4].

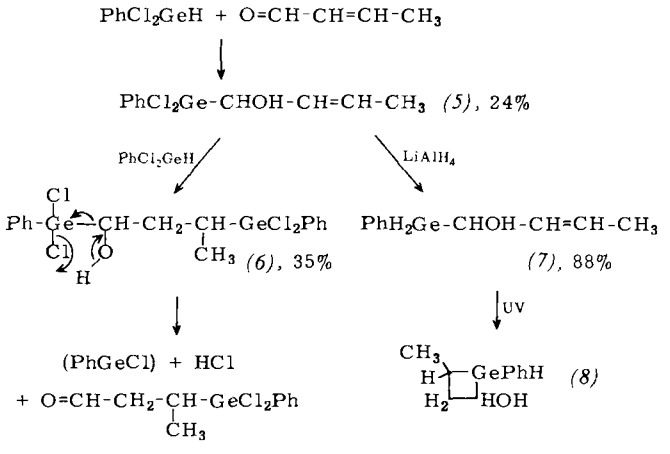


Table. Physical data for the germacycloalkanols *(4)*, *(8)*, and *(11)*.

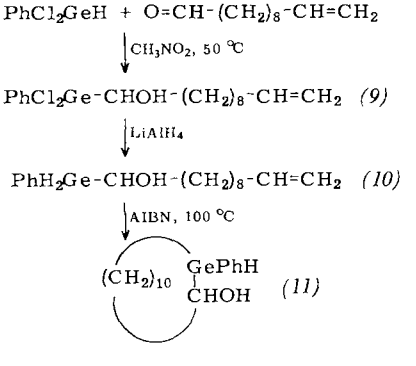
	(4)	*(8)*	*(11)*
B.p. (°C/torr)	$96/4\times10^{-2}$	$98-103/5\times10^{-2}$	$150-160/6\times10^{-2}$ (decomp.)
IR [a] (cm^{-1})			
νOH	3340	3300	3340
νGeH	2040	2030	2045
NMR [b] (ppm)			
δGeH	4.37	4.38	4.40
δHCO	3.45	3.45	3.48
δCH_2	1.0—1.80		
δCH_3		0.90—1.30	
Yield (%)	10	12	70 [c]

[a] Film.

[b] In CCl_4, $Si(CH_3)_4$ as internal standard; all signals are multiplets.

[c] Yield determined by NMR spectroscopy.

Reduction of *(5)* with $LiAlH_4$ gives 1-phenylgermyl-2-butenol *(7)* (b.p. 78 °C/5×10^{-2} torr) which has been characterized by IR and NMR spectroscopy. Unlike *(2)*, the alcohol *(7)* does not polymerize on heating. However, it is converted into 4-methyl-1-phenyl-1-germa-2-cyclobutanol *(8)* on UV irradiation (Table); polymeric products are also formed.



An addition of the same type is observed with 10-undecenal. The unstable phenyldichlorogermyl alcohol *(9)* is reduced by $LiAlH_4$ to phenylgermyl alcohol *(10)*, which cyclizes at 100 °C in the presence of azoisobutyronitrile to give 1-phenyl-1-germyl-2-cyclododecanol *(11)* (Table).

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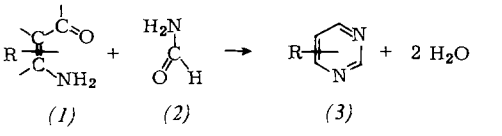
[3] *M. Massol, P. Rivière, J. Barrau*, and *J. Satgé*, C. R. Acad. Sci. Paris *270 C*, 237 (1970).

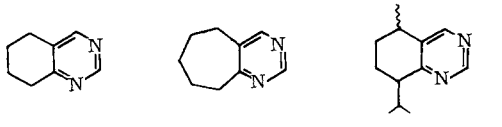
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Pyrimidines from *N,N*-Unsubstituted β-Enamino Carbonyl Compounds and Formamide

By *Eberhard Breitmaier*[*]

Not only *N*-alkyl and *N,N*-dialkyl β-enamino carbonyl compounds[1] but also *N,N*-unsubstituted β-enamino aldehydes and ketones (β-aminovinyl aldehydes and ketones) *(1)* undergo cyclocondensation with formamide *(2)* to give pyrimidines *(3)*. R may also be replaced by H or by part of a fused ring.





This reaction can be used for the synthesis of the pyrimidines *(3a)–(3j)* listed in the Table, of which *(3e)–(3j)* were hitherto inaccessible[2]. The heterocyclic compounds obtained were characterized on the basis of their identity with known pyrimidines and by elemental analysis and ^{1}H-NMR spectra. Thus, for example, the ^{1}H-NMR spectra of the 5-alkylpyrimidines *(3b)–(3g)* contain the peak due to the proton on C-2 at $\tau = 0.9$, and that due to the equivalent protons on C-4 and C-6 at $\tau = 1.35$ [in deuteriochloroform relative to tetramethylsilane as internal reference; intensity ratio: H-2: (H-4 + H-6) = 1:2]. These peaks are shifted upfield (H-2: $\tau = 1.0$–1.1; H-4: $\tau = 1.5$–1.6; intensity ratio: H-2:H-4 = 1:1) in the ^{1}H-NMR spectra of the bicyclics *(3h)–(3j)*.

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	(1)	(3)	Yield	B. p. (°C/torr)	Ref.
(a)	3-aminoacrolein	pyrimidine	60	124–126/760	[2]
(b)	2-methyl-3-aminoacrolein	5-methylpyrimidine	88	154–155/760	[1b, 2]
(c)	2-ethyl-3-aminoacrolein	5-ethylpyrimidine	83	175–176/760	[1b, 2]
(d)	2-isopropyl-3-aminoacrolein	5-isopropylpyrimidine	75	96–97/40	[1b, 2]
(e)	2-*n*-propyl-3-aminoacrolein	5-*n*-propylpyrimidine	81	68–69/11	—
(f)	2-*n*-butyl-3-aminoacrolein	5-*n*-butylpyrimidine	85	79–80/11	—
(g)	2-*n*-amyl-3-aminoacrolein	5-*n*-amylpyrimidine	92	94–95/11	—
(h)	2-aminomethylenecyclohexanone [7]	5,6,7,8-tetrahydroquinazoline	87	89–90/11	[8]
(i)	2-aminomethylenecycloheptanone [7]	5*H*-6,7,8,9-tetrahydrocyclohepta[*d*]pyrimidine	85	94–95/11	—
(j)	2-aminomethylene-3-methyl-6-isopropylcyclohexanone [7] [a]	5-methyl-8-isopropyl-5,6,7,8-tetrahydroquinazoline [a]	78	135–138/11 98–101/1	—

[a] Mixture of stereoisomers and optical isomers.

The method opens up an effective synthesis of interesting and hitherto difficultly accessible pyrimidines, such as *(3h)–(3j)*. It also provides supporting evidence for the mechanism proposed by *Bredereck*, *Gompper*, and *Morlock* for the synthesis of pyrimidines from 1,3-diketones and 1,3-dialdehydes[1a,3] since *N*,*N*-unsubstituted β-enamino carbonyl compounds are suggested to be the key intermediates in that synthesis.

Procedure:

Compound *(1)*[4–6] (0.1 mole) and formamide *(2)* (18 g) are refluxed with piperidinium acetate for 12–14 h in an oil bath at 140 °C. After cooling, the resulting yellow oil is poured into chloroform (50 ml). The lower phase, consisting of chloroform and the pyrimidine *(3)* is separated off, and the upper layer, containing formamide and water, is extracted with three 25-ml portions of chloroform. The united chloroform solutions are dried over anhydrous magnesium sulfate, filtered, and vacuum distilled (for results see Table).

2-Hydroxymethylenecycloalkanones required for the preparation of 2-aminomethylenecycloalkanones *(1h)–(1j)*[6] can be obtained from the corresponding cycloalkanones[7].

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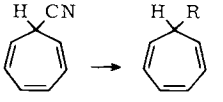
[8] *H. Bredereck, R. Gompper*, and *B. Geiger*, Chem. Ber. *93*, 1402 (1960).

Stable 2,4,6-Cycloheptatrien-1-ylmethyl Cations[1]

By *Werner Betz* and *Jörg Daub*[*]

Studies of stable 2,4,6-cycloheptatrien-1-ylmethyl cations should permit conclusions to be drawn regarding the effect of the substituent at C-1 on the cycloheptatriene⇌norcaradiene equilibrium[2]. Stable 2,4,6-cycloheptatrien-1-ylmethyl cations have not previously been described in the literature. Reaction of such cycloheptatriene systems that could be formulated as proceeding *via* cationic intermediates mostly give ring-contracted benzene derivatives[3–6].

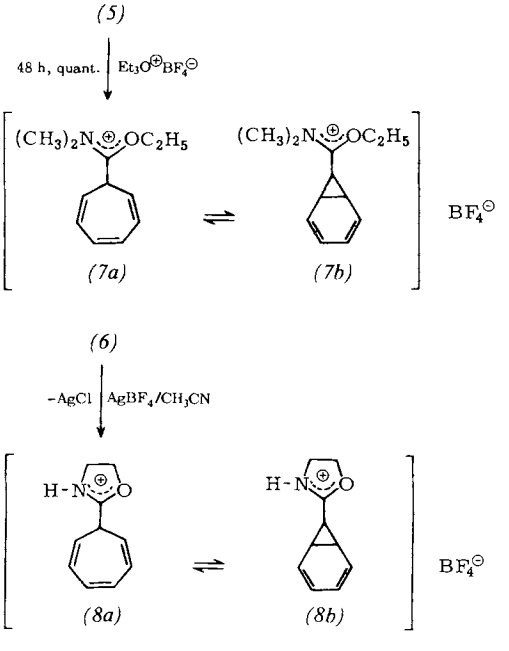
We have now been able to prepare 2,4,6-cycloheptatrien-1-ylmethyl cations, in which the positive charge is stabilized by an α hetero atom, from the carboxylic acid derivatives *(5)* and *(6)*, which are themselves accessible from 2,4,6-cycloheptatriene-1-carbonyl chloride *(4)* (Table 1). Our reaction route for preparation of *(3)* *via* compounds *(1)* and *(2)* has proved more effective than former methods[5,7,8].



(1) *(2)–(6)*

Reaction of *(5)* with triethyloxonium tetrafluoroborate or of *(6)* with $AgBF_4$ affords the oily complexes *(7)* and *(8)*, respectively.

The ^{1}H-NMR spectra (Table 2) furnish information concerning the structures of *(7)* and *(8)*. The τ values of the protons $H^{2,7}$ of *(7)* and *(8)*, which in both cases



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Table 1. Substituted cycloheptatrienes from 2,4,6-cycloheptatriene-1-carbonitrile *(1)*, b.p. 78—80/12 torr, which was prepared from tropylium tetrafluoroborate [a].

Cpd. [a]	R	Preparation	B.p. (°C/torr)
(2)	$COOCH_3$	HCl/CH_3OH	87/12
(3)	COOH	$CH_3OH/H_2O/NaHCO_3/NaOH$	76/0.005
(4)	COCl	as in ref. [8]	74/1
(5) [b]	$CON(CH_3)_2$	from *(4)* and $HN(CH_3)_2$	93—95/0.001
(6) [c]	$CONH(CH_2)_2Cl$	from *(4)* and 2 mole aziridine	m.p. 97 °C

[a] All compounds gave correct elemental analyses.
[b] $\nu CO = 1640\,cm^{-1}$.
[c] $\nu CO = 1650\,cm^{-1}$.

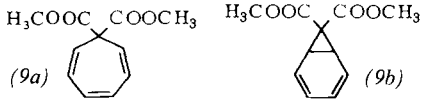
are shifted 0.4 ppm upfield from those of *(5)* and *(6)*, and a comparison of the chemical shifts of *(7)* and *(8)*

Table 2. Chemical shifts (τ values in ppm).

Cpd.	H^1	$H^{2,7}$	$H^{3,4,5,6}$	T (°C)
(5) [a]	7.7 (t)	4.6 (q)	3.2 —4.0	30
(6) [b]	7.4 (t)	4.5 (q)	3.2 —3.9	30
(7) [c,d]	6.85 [f]	5.3	3.4 —3.8	30
(7) [c]	[f]	5.0 (t)	3.15—3.7	−45
(8) [b,e]	6.9 (t)	4.9 [f]	3.25—3.8	30
(8) [b]	7.0 (t)	4.8 [f]	3.1—3.7	−42
(9a) [9]		4.28		
(9b) [9]		7.14		

[a] In CCl_4. [b] In $CDCl_3$. [c] In $CD_3C{\equiv}N$. [d] $>N-CH_3$: 6.65 (d); $-O-CH_2-CH_3$: 8.6 (t); 5.4 (q). [e] $>N-H$: 0; $>N-CH_2-$: 5.9 (t); $-O-CH_2-$: 4.95 (t). [f] τ values not accurately determinable.

with those of dimethyl 2,4,6-cycloheptatriene-1,1-dicarboxylate *(9a)* and dimethyl norcaradiene-7,7-dicarboxylate *(9b)*[9] show that neither the cycloheptatrienes *(7a)* and *(8a)* nor the norcaradienes *(7b)* and *(8b)* are present.



(9a) *(9b)*

However, these values would be expected for the equilibria *(7a)*⇌*(7b)* and *(8a)*⇌*(8b)*, the cycloheptatriene structure having the lower free energy in each case. The temperature dependence of the ^1H-NMR spectra of *(7)* and *(8)* is also a strong indication of dynamic equilibria.

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Inversion of Secondary Cyclic Grignard Compounds[**]

By *Adalbert Maercker* and *Reinhart Geuss*[*]

Inversion at the α-carbon atom of primary Grignard compounds can be detected by NMR spectroscopy[1]. Particular attention has been devoted to 3,3-dimethylbutyl (neohexyl) Grignard compounds (RMgX) and the corresponding dialkyl compounds (R_2Mg)[1a−1c], as well as 2-methylbutylmagnesium compounds[1d]. In contrast, inversion has not yet been observed with secondary Grignard compounds in spite of many efforts to detect it[1a,2]. Neither the reason for the slow (NMR time scale) inversion process of secondary carbanion centers nor the mechanism of inversion is known; the latter has been considered both as a bimolecular[1a,1d] and as a unimolecular ionization-recombination process[1b].

It was noted in NMR studies on carbanion rearrangements of cyclic homoallyl Grignard compounds[3] that the peak due to the α proton of 3-cyclohexenylmagnesium bromide *(1)* in THF, which lies in the TMS range as expected, is remarkably broad and unresolved at room temperature, whereas well resolved signals exhibiting fine structure were obtained at lower and at higher temperatures (Fig. 1). The high temperature spectrum, which

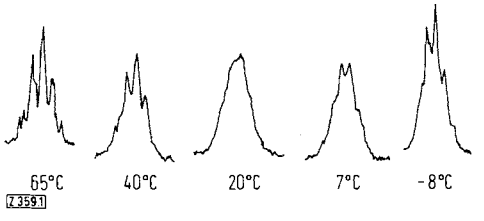


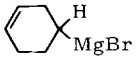
Fig. 1. Variation of the NMR signal (60 MHz) of the α proton of *(1)* with temperature; [D_8]-THF solution, 1.5 mole/l.

does not show any change above 70 °C (up to 110 °C), differed from the low temperature spectrum, which did not change below −10 °C. The occurrence of coalescence at 20 °C can only be explained by an inversion at the α carbon atom, *i.e.* this is the first example of a secondary Grignard compound whose α inversion is fast enough to be detectable by NMR spectroscopy. We assume that the inductive effect of the double bond between C-3 and C-4 enhances the electrophilicity of the magnesium, thus increasing the ease of replacement of the group in an S_E2 mechanism.

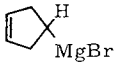
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

The spectrum of the 3-cyclopentenyl Grignard compound *(2)* also supports this concept: The α proton gives a clear quintet at $\tau = 10.2$ ($J = 10$ Hz) in ether and in THF. Thus, unlike the alcohol and the bromide, there is only one coupling constant to all four neighbors. This again suggests rapid inversion, although conclusive proof has not yet been obtained because the Grignard compound *(2)* is precipitated below −20 °C before the coalescence temperature has been reached[4]. However, it is quite reasonable to suppose that the five-membered ring Grignard compound *(2)* should invert more rapidly than the six-membered ring compound *(1)*, since in the former case



(1)



(2)

the −I effect of the double bonds can act from both sides *via* only two single bonds. It is therefore understandable that the coalescence point has still not been reached at as low a temperature as −20 °C. It is unlikely that homoallyl resonance plays a very important role in comparison with the inductive effects, particularly since the anion of *(2)*, even if σ overlapping with the π electrons of the double bond were permitted by the stereochemistry, would be a "bishomoantiaromatic" system[5]. In this connection it is interesting to note that primary, open-chain homoallyl Grignard compounds do not invert significantly more rapidly than the corresponding saturated compounds[6].

The inversion of the cyclic compound *(1)*, like that of primary Grignard compounds, depends on the medium[1,6]. It is particularly noteworthy that the rate of inversion is lowered not only on going from diethyl ether to THF but also on changing to more dilute solutions. This observation makes an ionization-recombination mechanism appear unlikely for the inversion of these Grignard compounds.

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[3] *A. Maercker* and *R. Geuss*, Angew. Chem. *82*, 938 (1970); Angew. Chem. internat. Edit. *9*, 909 (1970).

[4] The fact that the form of the quintet signal is independent of the temperature (−19 to +94 °C), of the solvent, of the concentration, and of the addition of magnesium bromide (also at 100 MHz), and does not change on going to the dialkylmagnesium compound, tends to dismiss any likelihood of an accidental equality of the *cis* and *trans* coupling constants.

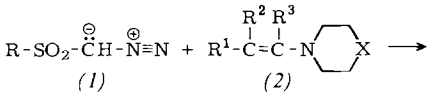
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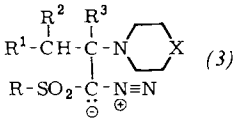
Electrophilic Alkylation of α-Diazosulfones with Enamines

By *A.M. van Leusen*, *B.A. Reith*, *R.J. Mulder*, and *J. Strating*[*]

The course of reaction of diazo compounds with enamines seems to be determined mainly by the type of diazo compound involved. During a study of the photolysis of α-diazosulfones[1] it was found that, without irradiation, α-diazosulfones *(1)* add to enamines. Surprisingly, the diazo group is not involved directly in this reaction, since the adducts are α-alkylated-α-diazosulfones *(3)*.



(1) *(2)*



(3)

The alkylated diazosulfones *(3)* are obtained easily in high yields, either by reaction of *(1)*[2] dissolved in an excess of *(2)* (neat), or by reaction of equimolar quantities of *(1)* and *(2)* in acetonitrile, for 2–5 days at room temperature in the dark. After removal of the solvent the residue is crystallized from methanol or ether/pet.ether.

	R	R^1	R^2	R^3	X
(3a)	*p*-Tolyl	CH_3	CH_3	H	O
(3b)	*p*-Tolyl	CH_3	CH_3	H	CH_2
(3c)	*p*-Tolyl	C_6H_5	H	H	O
(3d)	*p*-Tolyl	H	H	C_6H_5	O
(3e)	$C(CH_3)_3$	CH_3	CH_3	H	O
(3f)	$C_6H_5CH_2$	CH_3	CH_3	H	O

	Yield (%)	M.p. (°C)	IR (cm^{-1}) $\nu_{N\equiv N}$	IR (cm^{-1}) ν_{SO_2}
(3a) [a]	89	103—104	2067	1330, 1155
(3b)	77	82— 83.5	2072	1335, 1157
(3c)	50	109—111	2060	1308, 1150, 1120
(3d)	78	86— 87	2100	1330, 1155
(3e)	88	91— 92	2072	1315, 1155
(3f)	82	84— 85	2076	1318, 1120

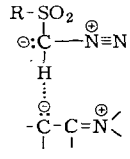
[a] NMR-Data (in $CDCl_3$) of *(3a)* [typical for the compounds *(3)*]: δ(R) = 2.43 (3 H/s), 7.73 (2 H/d), 7.33 (2 H/d), $J = 8$ Hz; δ(R^1) = 0.58 (3 H/d); δ(R^2) = 1.02 (3 H/d), $J = 6$ Hz; δ(H) = 1.1—2.3 (1 H/m); δ(R^3) = 2.95 (1 H/d), $J = 11$ Hz; δ(morpholino) 2.39 (4 H/m), 3.63 (4 H/m).

As far as diazo compounds are concerned, this is one of the very few examples in which an α-hydrogen becomes substituted by an alkyl group[3]. Moreover, the reaction can be considered as a nucleophilic addition at the C_α of an enamine. Such reactions are common for iminium salts, but not for the unprotonated enamines[4].

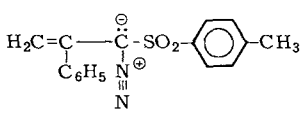
α-Diazoketones or α-diazoesters, bearing an α-hydrogen, react differently with enamines. Through a 1,3-dipolar cycloaddition involving the diazo function pyrazoles are formed eventually[5]. This difference may be explained as follows: The ability of the methine proton to act as a donor in hydrogen bonding presumably is larger in α-diazosulfones than in α-diazoketones[6]. In the case of α-diazosulfones some iminium salt character may be induced in the enamine through a hydrogen bond as indicated in *(4)*[7]. Thus, nucleophilic attack of the diazo carbon at the

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enamine C_α might be facilitated more for α-diazosulfones than for α-diazoketones.



(4)



(5)

The properties of the products *(3)* are remarkable also. Whereas α-tosyldiazoethane[1b] is thermally unstable and highly reactive, *(3a)* for instance is very stable under a variety of conditions. The diazo group in *(3a)* can be displaced only with difficulty.

With HCl in ether a salt is formed (according to NMR, protonation occurs at the morpholino nitrogen), in which the diazo function is still present. On exposure to the air, the salt slowly releases HCl and *(3a)* is recovered unchanged. Salt formation apparently occurs also in aqueous 2N HCl in which the water-insoluble *(3a)* dissolves. On treatment with NaOH *(3a)* is liberated again. By treatment of *(3a)* with Cl_2 in 2N HCl, however, the diazo group is replaced by two Cl atoms; at the same time the enamine function is hydrolyzed to give 1,1-dichloro-3-methyl-1-tosyl-2-butanone (m.p. 87°–89°C, 69% yield).

The HCl salt of *(3d)* is obtained similarly. When dissolved in chloroform at room temperature, this salt splits off morpholinium chloride to give a new, unsaturated α-diazosulfone, 3-diazo-2-phenyl-3-tosyl-1-propene *(5)*, isolated as a yellow oil and characterized as its triphenyl phosphazine (m.p. 138°–140°C, 65% overall yield).

The diazo group in *(3a)* can be reduced with $NaBH_4$ in methanol to give 1-hydrazino-3-methyl-2-morpholino-1-tosyl-1-butene (m.p. 133°–135°C, 93% yield). This α-β-unsaturated hydrazine is isomerized to the corresponding hydrazone (m.p. 134°–134.5°C, 63% yield) by treatment with 2N HCl.

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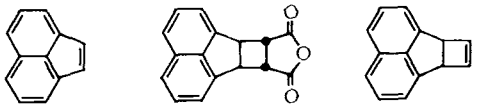
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A Heavy Atom Effect in the Photoreaction of Maleic Anhydride with Acenaphthylene

By *Willy Hartmann* and *Hans-Georg Heine*[*]

The property of heavy atoms to relax the forbidden transition between singlet and triplet states has been known for some time in spectroscopy[1]. On the other hand, the change in course of a photochemical reaction as a result of this phenomenon has only recently been studied and so far only been observed in the dimerization of acenaphthylene *(1)*[2], the addition of acrylonitrile to *(1)*[3], and the Rhodamine B sensitized oxygenation of 2,5-dimethylfuran[4]. We have now found a further example in our investigations of the addition of maleic anhydride to *(1)*.



(1) *(2)* *(3)*

Irradiation[5] of solutions of maleic anhydride and *(1)* in dioxane, acetone, or acetonitrile leads to formation of a copolymer[6] and/or the dimers of *(1)*[7]. If an halogenated solvent is used, the reaction proceeds differently; under otherwise similar reaction conditions a further product, the cycloadduct *(2)* m.p. 235–236°C, is formed. The yield of *(2)* increases proportionally with the atomic number of the halogen, and at the expense of the copolymer (see Table).

Table. Solvent dependence of the product distribution in the combined irradiation[5] of maleic anhydride and acenaphthylene.

Solvent	Yield (%) *(1)*-Dimer [a] [b]	Copolymer [b]	*(2)* [b]	Conversion of *(1)* (%)
Dioxane	97	–	–	17
Acetone	61	29	–	50
Acetonitrile	35	51	–	53
Dichloromethane	11	25	56	49
Dibromomethane	12	18	70	47
Iodomethane	13	–	81	47

[a] Mixtures of stereoisomers of different composition.
[b] Referred to unchanged *(1)*.

The IR spectrum (KBr) of *(2)* shows the characteristic bands for a saturated cyclic five-membered anhydride at 1790 and 1870 cm^{-1}. The NMR spectrum (CD_2Cl_2) contains signals at $\tau = 2.0$–2.5 (aromatic protons), 5.46 (benzyl protons), and 4.55 (cycloaliphatic protons) in the intensity ratio 3:1:1. In agreement with the spectroscopic data, oxidative decarboxylation of the adduct with $Pb(OAc)_4$/pyridine[8] affords the cyclobutene derivative *(3)*, m.p. 117.5–118.5°C, whose hydrogenation (ethylacetate/5% Pd-carbon) leads to the known[9] 6b,7,8,8a-tetrahydrocyclobut[*a*]acenaphthylene, m. p. 78.5–79.5°C. The *anti* configuration of *(2)* follows from the results of ozonolysis, oxidative treatment, and esterification with diazomethane to *cis,trans,cis*-1,2,3,4-tetracarbomethoxycyclobutane[10].

anti-6b,7,8,8a-Tetrahydrocyclobut[a]acenaphthylene-7,8-dicarboxylic anhydride (2)

After irradiation[5] of compound *(1)* (8.5 g) and maleic anhydride (15 g) in anhydrous dibromomethane (150 ml), 0.35 g (9%) of the *trans* dimer of *(1)* was separated from the irradiated mixture by filtration. Evaporation of the filtrate gave a solid residue which was digested twice with anhydrous ether (2 × 75 ml) to remove unchanged *(1)* (4.5 g) and maleic anhydride. On extracting the ether in-

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soluble part with boiling anhydrous benzene (150 ml), there remained 1.1 g (18%) of copolymer.

The benzene solution afforded, after concentration and multiple fractional crystallization from benzene or ethyl acetate, 4.3 g (70%) of *(2)*, m. p. 235–236 °C and 0.1 g (3%) of the *cis* dimer of *(1)* [yields based on 47% conversion of *(1)*].

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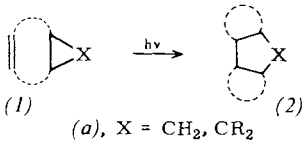
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Photochemical Olefin-Aziridine Cycloaddition[1][**]

By *Michael Klaus* and *Horst Prinzbach*[*]

Intramolecular $[2\pi+2\sigma]$ photocycloadditions between ethylene units and cyclopropane or oxirane units to give cyclopentane derivatives $[(1a)\rightarrow(2a)]$[2] or tetrahydrofuran derivatives $[(1b)\rightarrow(2b)]$[3] are valuable synthetic steps in preparative chemistry[4].



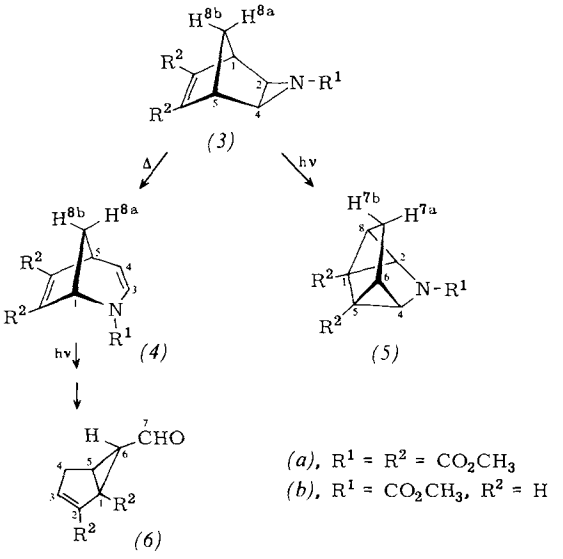
(1) *(2)*

(a), X = CH_2, CR_2
(b), X = O
(c), X = N-CO_2CH_3

Taking compound *(3a)* as an example, we shall now show that a similar type of valence isomerization between a CC double bond and an aziridine ring $[(1c)\rightarrow(2c)]$ can also be achieved photochemically[5].

The *exo*-aziridine *(3a)* is obtained *via* the triazoline by known methods from dimethyl bicyclo[2.2.1]heptadiene-2,3-dicarboxylate and methyl azidoformate[6]. Like the isocycle and oxaheterocycle, *(3a)* is rearranged on heating (160 °C, 3.0 g in 6.5 h) by cleavage of an exocyclic bond of the three-membered ring to give the bicyclic compound *(4a)*[7] (78% yield, colorless oil). Results of photolysis experiments are in accord with the structure deduced from spectroscopic data (cf. Table); after hydrolysis of the photoproduct, the aldehyde *(6a)* can be isolated. No di-π-methane rearrangement products could be detected.

A relatively rapid reaction takes place when *(3a)* is subjected to direct irradiation in O_2-free acetonitrile (−20 °C,

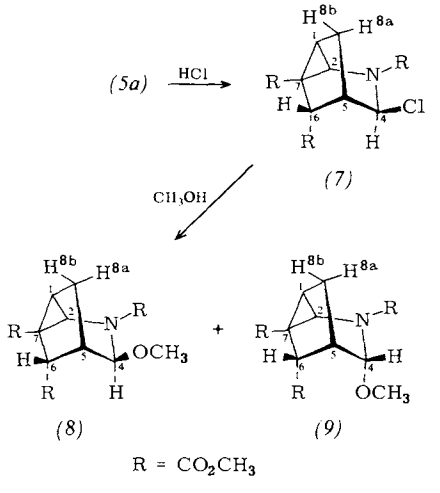


(3) *(4)* *(5)* *(6)*

(a), $R^1 = R^2 = CO_2CH_3$
(b), $R^1 = CO_2CH_3$, $R^2 = H$

5.0 g in 300 ml CH_3CN, 5.5 h) with vycor-filtered light from a high-pressure Hg vapor lamp; in addition to polymeric material and a small amount (3–5%) of hydrogenated products, the bishomopyrrole diester *(5a)* is formed as a colorless oil which crystallizes from ethyl acetate/pet. ether (50–55%). Conversion into *(5a)* has not been observed upon indirect excitation in acetone.

The tetracycle *(5a)* is thermally very stable and does not react with dimethyl acetylenedicarboxylate by addition to the bishomopyrrole moiety below 200 °C. On the other hand, it reacts almost instantaneously with HCl gas at room temperature to give *(7)*. On treatment with methanol a mixture of the isomeric compounds *(8)* and *(9)* (ratio ≈ 20:1) is formed.



(5a) *(7)* *(8)* *(9)*

R = CO_2CH_3

The structure of the photoproduct *(5a)* is evidenced by the chemical transformations to *(7)*, *(8)*, and *(9)* and confirmed by spectroscopic data. The stereochemistry of the addition of HCl and of methanol in *(7)* and *(8)* is apparent from $J_{5,6}$ and from the W-coupling $J_{4,8b}$ confirmed by double resonance. The absence of this W-coupling and the higher position of the H^{8a} signal compared to that of H^{8b} confirm the *endo* position of the methoxy group in *(9)*. Evidence for a primary excitation of the maleate chromophore in the isomerization $(3a)\rightarrow(5a)$ is provided by the finding that *(3b)* likewise affords *(4b)* thermally, but does not undergo a $[2\pi+2\sigma]$ cycloaddition to *(5b)* either upon direct or upon sensitized excitation.

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Cpd. [a]	UV [b]	NMR(τ) [c]											
M. p. (°C) (B. p. (°C/ 10^{-3} torr))	λ_{max} (nm, ε)	H^1	H^2	H^3	H^4	H^5	H^6	H^7 a	H^7 b	H^8 a	H^8 b	$-OCH_3$	J(Hz)
(3a) (124–125)	217 (6200) 231 (S, 5100)	6.59 (M)	6.90 (brS)		6.90 (brS)	6.59 (M)				8.21 (dM)	8.60 (dM)	6.28 6.37	$J_{8a,8b}=9.2$
(4a) (136–138)	217 (20700) 308 (1800)	4.63 (brM)		3.38 (dM)	4.94 (dD)	7.12 (M)				8.54 (dT)	8.27 (dM)	6.52	$J_{3,4}=8.0$; $J_{4,5}=6.5$; $J_{8a,8b}=11.0$; $J_{4,8b}=1.2$; $J_{1,8b}\approx J_{5,8b}\approx 4$; $J_{1,8a}\approx J_{5,8a}\approx 1$
(5a) 39–40 (150–155)	$\varepsilon_{210}=7800$		5.85 (D)		5.85 (D)		7.86 ("T")	8.20 (D)	7.77 (dT)	7.86 ("T")		6.33	$J_{2,8}=J_{4,6}=7.5$; $J_{6,7b}=J_{8,7b}=4.7$; $J_{7a,7b}=12.3$
(6a)	222 (4600)			3.40 (M)	6.80–7.31 (M)		8.34 (dD)	0.62 (D)				6.19 6.22	$J_{5,6}=4.5$ $H_{6,7}=6.2$
(7)		7.80 (dM)	5.73 (brD)		4.30 (dM)	≈7.3 (M)	6.63 (D)			7.37 (D)	8.08 (dM)	6.18 6.30	$J_{1,2}=8.1$; $J_{4,5}=4.0$; $J_{4,8b}<1$; $J_{2,4}<1$; $J_{5,6}=5.5$; $J_{2,6}\approx 1$; $J_{8a,8b}=12.5$; $J_{1,8b}\approx J_{5,8b}\approx 3.5$
(8)	$\varepsilon_{210}=4400$	8.01 (dM)	5.69 (brD)		5.18 (brD)	7.43 (M)	6.70 (D)			7.68 (D)	8.50 (dM)	6.31 6.39 6.44 6.60	$J_{1,2}=8.5$; $J_{4,5}=4.0$; $J_{5,6}=5.8$; $J_{8a,8b}=12.5$; $J_{1,8b}\approx J_{5,8b}\approx 4$
(9)	$\varepsilon_{210}=3900$	8.10–8.33 (M)	5.65 (brD)		5.41 (brD)	7.31 (M)	6.85 (D)			8.49 (D)	7.98 (dM)	6.25 6.32 6.41 6.79	$J_{1,2}=7.5$; $J_{4,5}=3.5$; $J_{5,6}=5.5$; $J_{8a,8b}=12.5$

[a] Satisfactory elemental analyses were obtained.
[b] In ethanol.
[c] In CCl_4, cpd. *(4a)* in C_6D_6 (+50°C), cpd. *(5a)* at 220 MHz (+60°C), cpd. *(7)* at +60°C, cpd. *(8)* in CCl_4/C_6D_6.

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Isocyanide Complexes of Thorium and Uranium Halides[**]

By *Franz Lux* and *U.-E. Bufe*[*]

In discussions of the bonding of actinoids particular interest attaches to the range of existence of their organometallic compounds. With one exception[1], the ligands in all the actinoid organometallic compounds hitherto described are in a negative oxidation state relative to the actinoid atom[2]. We have studied complexing with neutral ligands to form stable actinoid-carbon compounds and now report on the first isocyanide complexes of actinoids that contain no stabilizing π ligands such as are found in $(C_5H_5)_3U\cdot CNC_6H_{11}$[1].

Reaction of uranium tetraiodide (0.75 g, 1 mmole) with cyclohexyl isocyanide (1.25 ml, 10 mmoles) in anhydrous *n*-hexane at −5°C for 80 h, followed by filtration, washing of the residue with *n*-hexane (20 ml), and drying *in vacuo* (10^{-5} torr) – all operations being performed at −5°C – gave tetraiodotetrakis(cyclohexyl isocyanide)uranium(IV), $UI_4(CNC_6H_{11})_4$.

The compound is not noticeably sensitive to oxygen, but extremely so toward moisture. It can be kept for some time at 0°C, but gradually turns brown at room temperature. This aging process also results in a considerable reduction in solubility. The fresh complex is hardly soluble in *n*-hexane, moderately soluble in benzene, and dissolves readily in chloroform, acetone, methanol, *etc.* The initially yellow solutions gradually deposit a dark brown precipitate.

The instability of the compound in solution is also apparent from the following observations:

1) Reaction of uranium tetraiodide with a solution of cyclohexyl isocyanide in a small volume of benzene furnishes the compound directly in the solid state in the reaction mixture. However, owing to the partial decomposition of the portion dissolved in benzene the product

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obtained after filtration and washing in benzene is probably less pure than that prepared in hexane suspension.

2) Reaction of uranium tetraiodide with cyclohexyl isocyanide in chloroform rapidly yields an orange-yellow solution. The complex is precipitated by addition of carbon tetrachloride or *n*-hexane. These products are dark in color and not analytically pure.

The complex closely resembles $Pd(CNC_6H_{11})_2$[3] in its chemical and physical properties.

In the IR spectrum (KBr disk) the ν(NC) band appears at 2190 cm^{-1} and is thus shifted by 55 cm^{-1} toward higher wave numbers ($C_6H_{11}NC$: ν(NC) = 2135 cm^{-1}[4]), in full agreement with the general tendency of ν(NC) to be shifted toward higher frequencies or considerably less toward lower frequencies in isocyanide complexes having a positively charged metal atom than in metal(0) complexes[5]. This suggests that the uranium-carbon bond has considerable σ-donor character. In the limiting case of a pure σ-donor bond of isocyanide[6] in $(C_6H_5)_3B{\cdot}CNC_6H_{11}$ (ν(NC) = 2255 cm^{-1}[7]) the bond shift toward higher wave numbers amounts to 120 cm^{-1}. In $UI_4(CNC_6H_{11})_4$ the U—C bond therefore has a back-bonding component.

In agreement with the argumentation above, ν(NC) = 2160 cm^{-1} is shifted only 25 cm^{-1} toward higher wave numbers in $(C_6H_5)_3U{\cdot}CNC_6H_{11}$, which is a U^{III} complex. Thus, as suggested by the ready oxidation of U^{III} to U^{IV}, a relatively large contribution by uranium → isocyanide back bonding can be assumed[1].

If IR measurements are repeated on the same sample the intensity of the characteristic ν(NC) band decreases until the band finally disappears altogether. At the same time the KBr disk turns dark and loses its isocyanide odor.

Similarly, thorium tetraiodide, uranium tetrabromide[8], uranium tetrachloride, and uranyl chloride react with cyclohexyl isocyanide in *n*-hexane to give ivory-colored complexes having ν(NC) = 2194, 2193, 2196 and 2213 cm^{-1} respectively.

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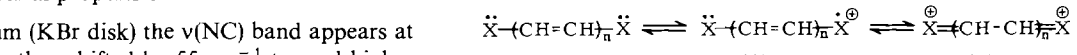
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[8] Unpublished work by *A. Kühnl.*

The Position of Equilibrium in Vinylogous Two-Step Redox Systems

By *Siegfried Hünig, Friedrich Linhart,* and *Dieter Scheutzow*[*]

Redox systems of general structure *(1)* allow one-electron transfers in two discrete steps[1-3], whereby the redox equilibrium [eq. (1)] can lie strongly on the side of the radical cation ("violene"[4]) $(1)_{sem}$ (*K* so far up to 10^9).



$$red + ox \rightleftharpoons 2\,sem$$
$$K = [sem]^2/[red][ox] \qquad (1)$$

Using previously estimated values[5] as a starting point for further examination of such systems, *P. Čársky* and *R. Zahradník*[6] have been able to detect a linear relationship between log *K* of vinylogous systems *(1)* and the change of π electron energy calculated according to

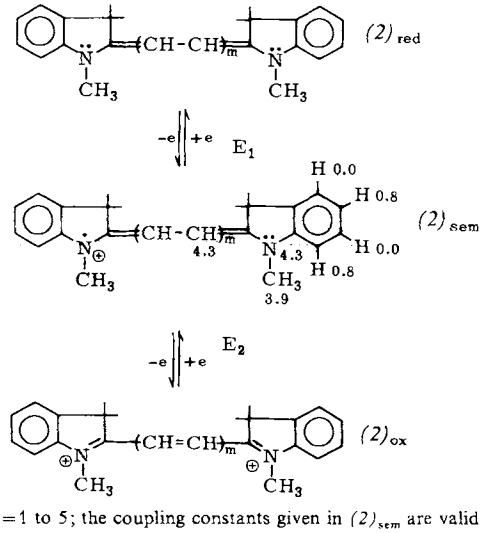
$$E_\pi^{ox} + E_\pi^{red} - 2\,E_\pi^{sem} = J_{mm}\ ^{[7]}$$

if it is assumed that solvation effects can be neglected.

This assumption holds true in the case of the previously investigated systems *(1)* ($n = 1$ to 3), in which X is a part of an (aromatic) ring[6].

In order to investigate the behavior of π systems which are not directly coupled to aromatic rings, we synthesized the vinylogous compounds $(2)_{red}$ and $(2)_{ox}$ ($n-1=m=1$ to 5) and produced $(2)_{sem}$ ($m = 1$ to 5) by comproportionation of $(2)_{red}$ and $(2)_{ox}$ in acetonitrile (Scheme 1)[8,9]. The species $(2)_{sem}$ ($m = 1$ to 5) show characteristic absorption and ESR spectra with pronounced hyperfine structure in the case of the lower members[8]. As expected the $>C(CH_3)_2$ group does not participate in the delocalization of the single electron. The ESR spectrum of $(2)_{sem}$ ($m = 1$) can be readily simulated using the quoted coupling constants without consideration of this group (Fig. 1)[9].

Thus *(2)* behaves as a pure vinylogous system, which, in addition, exists as the longest series known to date. For $m = 1$ to 3, *K* can be obtained from the polarogram[10]; for $m = 3$ to 5 it is obtained from the extinctions of the comproportionation solution[11]. As can be seen in the Table, log



Scheme 1. $m = 1$ to 5; the coupling constants given in $(2)_{sem}$ are valid for $m = 1$.

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	(2), m = 1	2	3	4	5
E_1 [a]	−60	−58	—	—	—
E_2 [a]	+280	+90	—	—	—
E_m [a, b]	+110	+16	−30	−50	−67
Amount of $(2)_{sem}$ (%)	99.8	90	48	6	< 1
log K	5.9	2.5	0.5	−1.7	−3.5
J^{sem}_{mm} (eV) [c]	4.02	3.68	3.40	3.16	2.96

[a] E(mV) in CH_3CN; Ag/AgCl reference electrode.
[b] $E_m=(E_1-E_2)/2$. [c] J^{sem}_{mm} = Repulsion integral.

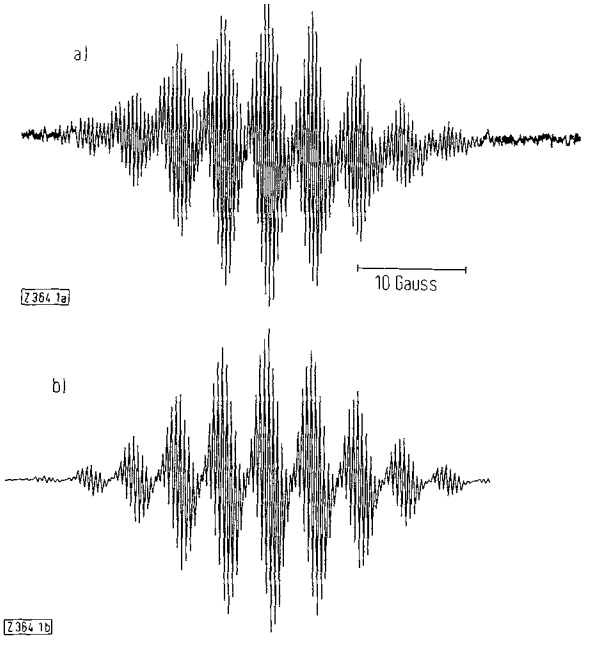


Fig. 1. a) ESR spectrum of $(2)_{sem}$ ($m=1$) in acetonitrile; b) simulated spectrum.

K, and consequently the thermodynamic stability of $(2)_{sem}$, rapidly decreases with increasing chain length, *i.e.* the difference between E_1 and E_2 becomes progressively smaller.

As in the case of previously investigated violenes[6], K is scarcely influenced by solvation effects, thus indicating the linear relation between log K of *(2)* and J^{sem}_{mm} for $m=1$ to 5.

The significance of these calculations for predictions about other redox systems of type *(1)* is thus more apparent than heretofore. In particular, it has been established that J^{sem}_{mm} should be greater than 4 eV if isolation of $(1)_{sem}$ in substance is desired (*i.e.* log $K>3$)[6].

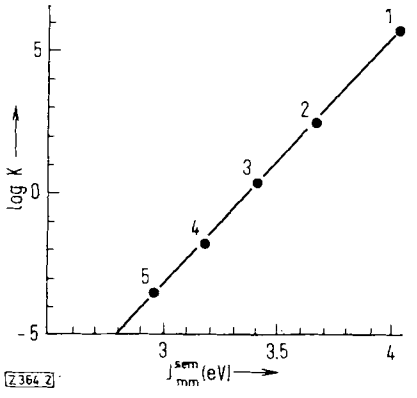


Fig. 2. Correlation between log K and J^{sem}_{mm} for *(2)*, $m=1$ to 5.

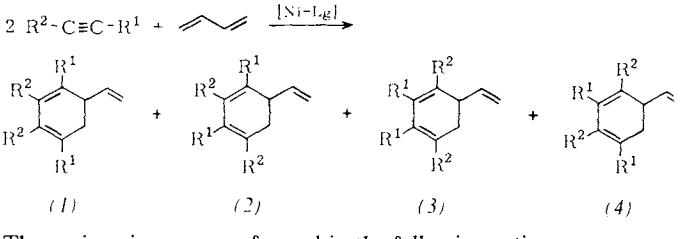
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Preparation of Substituted 5-Vinylcyclohexa-1,3-dienes and Tricyclo[2.2.2.0^{2,6}]oct-7-enes

By *Paul Heimbach*, *Klaus-Jürgen Ploner*, and *Frank Thömel*[*]

In our last communication concerned with the mixed oligomerization of butadiene and alkynes[1] we mentioned, *inter alia*, the formation of 5-vinylcyclohexa-1,3-diene *(1a)* from phenylacetylene and butadiene (molar ratio 1:5 at start of reaction) at −10 °C in the presence of a nickel^0-triphenylphosphane catalyst in 25% yield[2].

We have now found[3] that butadiene reacts with alkyl- or aryl-substituted acetylenecarboxylic esters under the above conditions to give substituted 5-vinylcyclohexa-1,3-dienes *(1)–(4)*.



The various isomers are formed in the following ratios:

$$(1b):(2b) = 1.2:1.0$$
$$(1c):(2c) \approx 1:1$$
$$(1d):(2d):(3d):(4d) = 1.7:1.4:1.0:6.7$$

At 180 °C the 5-vinylcyclohexa-1,3-dienes *(b)–(d)* rearrange quantitatively to the tricyclo[2.2.2.0^{2,6}]oct-7-enes. This rearrangement has already been described for unsubstituted 5-vinylcyclohexa-1,3-diene[4,5] and for a derivative having a disubstituted vinyl group[6]. The equilibrium mixture of *(1a)* and *(5a)* contains the two components in the ratio 70:30 at 180 °C.

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[1] *S. Hünig*, Liebigs Ann. Chem. *676*, 32 (1964).

[2] See review by *S. Hünig, H. Balli, H. Conrad, H. Friedrich, J. Gross, G. Kiesslich, G. Ruider, G. Sauer*, and *D. Scheutzow*, Pure Appl. Chem. *15*, 109 (1967).

[3] *S. Hünig* and *H. Quast* in: Optische Anregung organischer Systeme. Verlag Chemie, Weinheim 1966, p. 184. The same considerations apply to $red^{2\ominus} + ox \rightleftarrows 2\ sem^{\ominus}$.

[4] Previous communication: *S. Hünig* and *J. Gross*, Tetrahedron Lett. *1968*, 2599; for further examples see ref. [3].

[5] *N.S. Hush* and *J. Blackledge*, J. Chem. Phys. *23*, 514 (1955).

[6] *P. Čársky, S. Hünig, D. Scheutzow*, and *R. Zahradník*, Tetrahedron *25*, 4781 (1969).

[7] E_π: total π-electron energy of system considered; J_{mm}: Coulombic repulsion integral of the singly occupied MO.

[8] $m=1$, 3–5, Dissertation *F. Linhart*, Universität Würzburg 1970.

[9] $m=2$, Dissertation *D. Scheutzow*, Universität Würzburg 1966. Simulated by *F. Linhart* and *D. Scheutzow* using the "Hyfralg" program on the EL × 8 Computer of the computing center of Würzburg University.

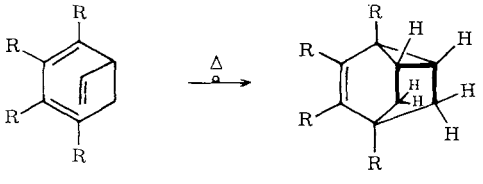
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[11] This simple procedure (see ref. [8]) affords minimum values for log K that are known to deviate from the polarographic values by up to ±20% in similar cases.

	R^1	R^2	Products	Overall yield (%) [2]
a	C_6H_5	H	*(1a)*	25
b	$COOCH_3$	CH_3	*(1b), (2b)*	87 [a]
c	$COOC_2H_5$	C_4H_9	*(1c), (2c)*	≈80 [a]
d	$COOCH_3$	C_6H_5	*(1d)–(4d)*	76 [a]
e	CH_2OCH_3	CH_2OCH_3	*(1e)*	
f	CH_3	CH_3	*(1f)*	

[a] The yields are 80–95%, based on reacted butadiene at 15 to 20%.

All the tricyclo[2.2.2.0^{2,6}]oct-7-enes *(5)–(8)* prepared from butadiene and alkynes *via (1)–(4)* have a plane of symmetry. Their IR, ^{1}H-NMR, and mass spectra confirm the structures given (see Table).



(1)-(4) *(5)-(8)*

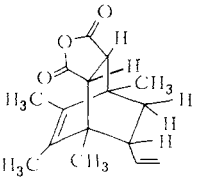
analogous to *(1)-(4)*

Table. Chemical shifts of the protons in the three-membered ring and the methylene groups of tricyclo [2.2.2.0^{2,6}]oct-7-ene (HA-100). The coupling of the methylene protons amounts to ≈11–12 Hz. In a number of compounds a weak coupling (≈1 Hz) of one proton of the methylene groups with the protons of the three-membered ring could be detected by extension of the spectrum. Compound *(7d)* was not isolated: assignment on the basis of the retention behavior in the gas-chromatographic examination of the reaction product prior to recrystallization.

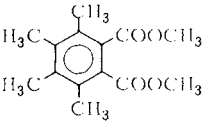
Cpd.	Protons in three-membered ring τ (ppm)	Protons in methylene groups τ (ppm)
(5a)	8.09	8.02 and 8.13; 8.65 and 8.76
(5b)	7.96	8.10 and 8.22; 8.73 and 8.84
(6b)	7.84	8.48 and 8.60; 8.93 and 9.04
(5c)	7.96	8.04 and 8.16; superimposed
(6c)	7.84	8.43 and 8.55; superimposed
(5d)	7.69	7.78 and 7.90; 8.27 [a] and 8.39 [a]
(6d)	7.55	7.87 and 7.98; 8.16 and 8.27
(8d)	7.94	7.78 and 7.90; 8.27 [a] and 8.39 [a]
(5e)	8.53	8.40 and 8.52; 9.10 and 9.22
(5f)	8.98	8.75 and 8.86; 9.19 and 9.30

[a] Weak splitting.

The conditions of the catalytic reaction exert a considerable influence on the course of the reaction. If phenylacetylene, for example, is added dropwise at 40 °C to a benzene solution of the catalyst [Ni^0-$P(C_6H_5)_3$] that is saturated with butadiene, the yield of *(1a)* can be increased from 25 to 78%[2]. 1,4-Dimethoxy-2-butyne reacts with



(9)



(10)

butadiene in the presence of Ni^0-tricyclohexylphosphane-catalyst at 20 °C to give *(1e)* in 26% yield. In the presence of a nickel catalyst having no phosphorus-containing ligands[7], slow addition of butadiene to 2-butyne at 30 °C gives *(1f)* in about 20% yield.

Both the 5-vinylcyclohexa-1,3-dienes and the tricyclo-[2.2.2.0^{2,6}]oct-7-enes react with dienophiles. At 20 °C, *(1f)* reacts with maleic anhydride to give the adduct *(9)*. *(5f)* reacts at 40 °C with dimethyl acetylenedicarboxylate to give *(10)*; any possible intermediates have so far defied detection.

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German version: Angew. Chem. *83*, 285 (1971)

[1] *W. Brenner, P. Heimbach, K.-J. Ploner,* and *F. Thömel,* Angew. Chem. *81*, 744 (1969); Angew. Chem. internat. Edit. *8*, 753 (1969).

[2] Yields based on reacted alkyne at approx. 100% conversion.

[3] Part of Dissertation by *F. Thömel,* Universität Bochum 1970.

[4] *W. von E. Doering* and *W.R. Roth,* Tetrahedron *19*, 715 (1963).

[5] *W.R. Roth* and *B. Peltzer,* Liebigs Ann. Chem. *685*, 56 (1965).

[6] *K. Alder et al.,* Liebigs Ann. Chem. *593*, 1 (1955).

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CONFERENCE REPORTS

Investigations of Reactions and Phase Transformations with a Novel X-Ray Camera

By *Arndt Simon*[*]

By suitable modification of the X-ray recording technique it is also possible to use the high resolution Guinier method for the investigation of substances that are extremely sensitive to air. The sample to be examined is fused in a Mark tube which is arranged parallel to the focal line of the monochromator on the focusing circle of the film chamber. With the aid of a sensitive control device, structural changes in the sample with temperature can be determined very accurately (±0.02 °C between −190 and 400 °C).

This method has been used in an investigation of the phase transformations occurring in solid halogen hydrides. With the modified apparatus it is possible, especially in the case of HBr, to detect all the transformations expected from the calorimetric behavior (orthorhombic ⇆ orthorhombic ⇆ cubic ⇆ cubic). Interpretation of the data obtained by X-ray crystallography would suggest that

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[1] *E. Rengade,* Bull. Soc. chim. France (4), *5*, 994 (1909).

intermolecular interactions over a wide range play an important role in the course of these transformations.

The modified apparatus proved particularly useful for the investigation of the phases in alkali metal suboxides. With additional aid of a sensitive DTA arrangement, existence of all the suboxides designated by *Rengade*[1] as Cs_7O, Cs_4O, Cs_7O_2, and Cs_3O could be established. The presently found compositions deviate, in certain cases quite distinctly, from those previously reported in the literature; the Cs_3O phase has a wide range of homogeneity. The occurrence of such suboxides is not confined to cesium; well-defined suboxides of rubidium have also been observed. In the latter case, however, the investigation is rendered much more difficult by the peritectic formation of Rb_2O at *ca.* 40 °C. In order to gain more detailed information about the suboxide phases, we have begun a series of X-ray crystallographic investigations on single crystals.

Lecture at Kiel on December 10, 1970 [VB 270 IE]
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Heterocycles from C_3 Systems and Sulfur

By *Friedrich Boberg*[*]

1,2-Dithiacyclopenten-ones, -thiones, -imines, and 1,2-dithiolium compounds can be prepared from allyl compounds and sulfur. 1,2-Dithiacyclopentenimines are also formed from 3-chloro-1,2-dithiolium compounds and *N*,*N*-dichloro compounds having electron attracting groups attached to the nitrogen (sulfonyl, alkoxycarbonyl, carbonyl) with elimination of chlorine. The systems are described by apolar and polar resonance structures (positive charge on the heterocycle, negative charge on the exocyclic heteroatom) in which electron shifts by substituents in position 5 have to be considered. Dipole moments of 1,2-dithiacyclopentenones and -thiones confirm these concepts. Information about the distribution of charge in the heterocycle is provided by chlorine exchange with $[^{36}Cl]$-$SbCl_3$ and $[^{36}Cl]$-$AlCl_3$, which, in the case of 3,4,5-trichloro-1,2-dithiolium chloride, preferentially takes place at the 3- and 5-positions.

1,2-Dithiacyclopentenones react with preservation of the heterocycle and with ring cleavage. The position of substitution is in agreement with theoretical concepts. S^{2-}, OH^-, RO^-, and R_2NH open the heterocycle between the carbonyl group and ring sulfur and reaction with Grignard compounds leads to ring cleavage at the disulfide bridge. The primary cleavage product reacts further to give various types of compounds, the substituents in the 4- and 5-positions of the 1,2-dithiacyclopentenone being of importance. The primary cleavage products from the reaction of RO^- with 1,2-dithiacyclopentenones containing Cl in position 4 or 5 undergo intramolecular or intermolecular elimination of Cl^- to give other sulfur heterocycles. The following products have been established: 1,2,5-trithiacycloheptadienes, 1,4-dithiacyclohexadienes, 1,2-dithiacyclohexadienes or the valence tautomeric dithioamides (unknown) and thiophenes from 4-chloro-1,2-dithiacyclopentenones; 1,2,4,5-tetrathiacyclohexanes, 1,2,4-trithiacyclopentanes, 1,3-dithiacyclobutanes, and 1,3-dithiacyclopentenes from 5-chloro- or 5-sulfonyl-1,2-dithiacyclopentenones[1]. The intermolecular mechanism is excluded in the case of the 1,2-dithiacyclohexadienes. The thiomalonic acid derivatives obtainable by reaction of 5-amino-1,2-dithiacyclopentenones with Grignard compounds are starting materials for the preparation of aminopyrazolinones and methylenebenzothiazoles.

Attempts to prepare the thiacyclopropene system were without success.

Lecture at Hannover on January 21, 1971 [VB 269 IE]
German version: Angew. Chem. *83*, 216 (1971)

[1] *J. Bader*, Helv. Chim. Acta *51*, 1421 (1968).

Electronic and Molecular Structure of Coordination Compounds of Transition Metals as Derived from Their Optical Properties

By *H.-H. Schmidtke*[*]

The gain in energy on formation of chemical bonding between central ions (electron acceptors) and ligands (donors) of a complex results from resonance properties of the electrons and from electrostatic interactions between the atoms and ions participating in the molecule. While the molecular orbital theory takes account of both effects, ligand field theory can only describe the electrostatic component of the bond. The ligand field theory satisfactorily accounts for the high- and low-spin behavior of the complexes that finds experimental expression in, for example, their magnetic behavior or their electronic spectra. However, the utility of the theory is limited once results are required that are not of a purely qualitative nature. For instance, no explanation is forthcoming of the existence of the spectrochemical series, in which some neutral ligands possess a stronger ligand field than charged ligands. The shortcomings of the theory are attributable to the overemphasis placed on electrostatic effects in the description of the electronic structure.

The angular overlap model, whose parameters are symmetry-orbital adapted and therefore better fitted to the molecular orbital theory, provides a better interpretation of experimental data. This model represents a semi-empirical theory which takes into account second order perturbation terms and which is of comparable quality to the Pariser-Parr theory. It is particularly suitable for the interpretation of spectra of low-symmetry coordination compounds with significantly covalent bonding and for the assignment of geometric isomers (*e.g.*, interpretation of the spectra of hydroxo complexes, assignment of the three geometric isomers of bis(L-histidinato) complexes). Mention should also be made of the assignment of linkage isomers, such as *S*- and *N*-bonded thiocyanate, on the basis of the electronic spectrum. Information about the mode of bonding is provided by both the ligand field theory and the charge transfer spectrum. The latter case is concerned with the transfer of ligand electrons to the d shell of the central ion. Assignment of linkage isomers is possible on the basis of differing optical electronegativities for *S*- and *N*-bonded thiocyanate.

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The Chemistry of Learning

A one day symposium on "The Chemistry and Biology of Memory" was held at the 137th Conference of the American Association for the Advancement of Sciences (December 26—31, 1970 in Chicago) under the chairmanship of *W.L. Byrne.*

A. M. Golub (University of Waterloo, Ontario, Canada) reported on experiments performed on 45 rats which had been trained in an automatic one-way avoidance box designed by *Tenen.* RNA was extracted from the brains of trained animals with phenol and then analyzed by gradient centrifugation. Most of it was represented by ribosomal RNA, which in general contains no information. When these RNA preparations were injected into the recipient animals, significant transfer effects were observed between the second and fifth day after the injection: the recipient animals immediately used the escape route in a Tenen apparatus on occurrence of conditioning stimuli although they had never been subjected to an electric shock. The effect of the intracranial injection is dependent on dose; the effect is better after the application of 0.25 brain equivalents than after 0.5 equivalents. The results are more impressive when rest periods have been given to the animals during the training.

E.J. Fjerdingstad (Brain Research Institute, Memphis, Tenn.) uses a light avoidance shock procedure similar to that described by *Agranoff* in 1963 for the group training of goldfishes; the fishes have to learn to swim rapidly under a barrier into the other half of the training tank when a light signal appears, otherwise they receive an electric shock. After 12 days' training RNA was extracted from the brains of the fishes by a method described by *Golub.* 30 micrograms of RNA, corresponding to one brain equivalent, is injected intracranially into recipient fish; when twice as much material is injected into the recipients the results become rather doubtful.

A second study reported by *Fjerdingstad* concerned the transfer of audiogenic seizures. According to a report by *Henry* (1967), some mice suffer seizures on being subjected to sonication, which under certain circumstances can lead to death. A mouse strain resistant to audiogenic seizures can be made sensitive by a single sonication of 60 seconds duration on the 16th day after birth, which is assumed to be the first day of hearing in the animals' life. When such recipients are sonicated on their 21st day of life they immediately die from seizures. Spontaneously insensitive animals can be made sensitive to sonication by injecting them with 0.006 equivalents of brain homogenate from artificially sensitized animals. The question has been raised by the author whether this means a real learning rather than priming of new-born animals.

The lecture given by *G. Ungar* (Baylor College of Medicine, Houston, Texas) was the most exciting paper given at the symposium. Rats, which normally prefer a dark part of their cage to an illuminated area, have been trained by an electric shock procedure to avoid the dark. From 4000 trained rats, 5 kg of brain were collected. The intraperitoneal injection of a homogenate prepared therefrom into untrained recipients made these animals stay in the illuminated part of the cage. The transfer active material can be purified chromatographically. 300 micrograms of a peptide consisting of 15 amino acids have been obtained. *Desiderio* (Houston) has been able to determine the primary structure of it by mass spectrometry.

W. Parr (Tübingen and Houston) has used the Merrifield solid phase technique for the synthesis of this peptide which has been named "Scotophobin". The following peptide showed 100% of biological activity compared to that of the natural material isolated from trained brains.

Ser—Asp—Asn—Asn—Gln—Gln—Gly—Lys—Ser—Ala—Gln—Gln—Gly—Gly—Tyr—NH_2[*].

In order to gain more information about the chemical nature of such memory transferring peptides two new procedures have been started for mass training of animals: 3000 rats will learn the sound habituation procedure and 20000 goldfishes are to be trained for color discrimination by the procedure described by *Zippel* and *Domagk. Ungar* has found that goldfish are able to distinguish between green and blue colors when the maximum absorption differs by only 30 nm.

O. Wolthuis (Medical Biological Laboratory, Rijswijk, Netherlands) has trained rats in a fully automated system in which the animals drink only when a light or an acoustic stimulus is offered. Total brain homogenates prepared from such trained donors will change significantly the behavior of the recipient animals. A stimulus specific transfer of acquired information seems to be possible.

J. Daliers (UCB-DIPHA, Brussels, Belgium) has studied the phenomenon of memory with the aid of the spinal cord fixation time: When one hemisphere of the cerebellum of an anesthetized rat is removed, the rat will show an asymmetry of its hind legs; on the side of the removed hemisphere the hind leg shows a hypertonic flexion, whereas the contralateral side rests in hypotonic extension. This asymmetry disappears when the spine is dissected within 35 minutes after end of narcosis; if the dissection is carried out after 45 minutes or later the asymmetry will persist. Apparently the animal has learned something during this period. When brain extract—prepared by extraction with organic solvents—from donors which have spent a certain time in asymmetry is injected into animals at the onset of narcosis these recipient animals will exhibit persistent asymmetry of the hind legs even when the spine is dissected after 35 minutes. It is concluded that immediately after the lesion there is a progressive biosynthesis of one or more compounds in the brain, the intraperitoneal injection of which facilitates the production of asymmetry. The extract was found to be specific for a left side or right side lesion of the cerebellum. Injection of such extracts does not interfere with the recipient rats' learning in a watermaze.

G.F. Domagk (Louvain, Belgium) and *H.P. Zippel* (Göttingen, Germany) reported on the transfer of acquired information in goldfish experiments. Untrained goldfish show strong preference for red light whereas green light is disliked. On combining the two stimuli these effects are even enlarged. In a shock-free procedure, with feeding of Tubifex worms as the reinforcement, the fish can be trained to prefer green light even when the latter is offered with red light as a competing stimulus. Brain extract prepared from fish trained by this procedure is injected intraperitoneally into naive red-preferring fish. The recipients, who have never in their life received food together with green light, develop a rather strong preference for green which lasts for about a week; if no reinforcement is offered during this test period the memory decays.

[*] The terminal carboxy group is amidated.

Since training periods of up to five to seven weeks are required in order to get well trained donors other training procedures have been tried. It has been found that fish spontaneously prefer certain tastes, whereas other chemical compounds are strongly disliked. Quinine or acetic acid, both spontaneously disliked, have been used as the conditioning stimulus after the fishes were trained to react positive to either of these stimuli. Even when glucose is offered as a competing spontaneously preferred stimulus, the fish had learned after five days to react positive to either quinine or acetic acid. Brain extract prepared from either kind of donor made the recipients go specifically for the taste offered as the conditioning stimulus during the training period. It was shown that the acquired information is strictly related to the stimulus used during the training procedure. The memory for taste training lasts for about one week, whereas fishes that have learned the same tasks by active training can remember this task up to three months. Evidence is presented that "double transfers" are possible, *i.e* the donor fish can been trained to react positive to a color as well as to a taste stimulus.

J.H. Levan (Chicago, USA) reported on investigations with mice, which prefer a 1% saccharine solution to water if both are offered simultaneously. When after a certain observation period the animals are treated with x-ray or gamma radiation, they reverse their drinking habit: now water is strongly preferred to the simultaneously offered saccharine solution. This aversion towards saccharine could be induced in non-irradiated animals by the injection of brain extracts prepared from irradiated donors. Such a transfer effect was not observed after injection of extract prepared from blood but positive transfer has been seen with extracts prepared from liver and spleen tissues of trained donors. This latter observation raised an interesting discussion about the possible distribution of memory transfer factors over the whole body.

[VB 272 IE]
German version: Angew. Chem. *83*, 257 (1971)

Trimethylsilyl- and Triphenylsilyl-Substituted Dyes

By *Heinrich Hopff*[*]

Trimethylsilyl- and triphenylsilyl-substituted aromatic compounds are now readily accessible *via* the Wurtz-Fittig synthesis. Permanganate oxidation of 3- and 4-trimethylsilyl-*o*-xylene leads to the previously unknown trimethylsilylphthalic acids which have been used for the synthesis of phthaleins, phthalocyanines, and quinophthalones. Introduction of the trimethylsilyl group causes a slight deepening in color, a noticeable increase in the solubility in organic solvents, and in certain cases, much better light-fastness. The advantage of such properties is particularly evident in the coloration of plastics and in "solvent dyeing".

Trimethylsilylindigo could only be obtained from the corresponding *o*-nitrobenzaldehyde by condensation with acetone in alkaline solution according to the method of *A. v. Baeyer*. 6,6'-Bis(trimethylsilyl)dithioxo-β,β'-isoindigo was prepared by reaction of trimethylsilylphthalodinitrile with hydrogen sulfide and ammonia. A larger number of trimethylsilyl-substituted mono-, di-, tri-, and tetracarboxylic acids were used for the synthesis of anthraquinone vat dyes. Trimethylsilyl-substituted anilidocyanuric chlorides were used for the preparation of triazinylaminoanthraquinone vat dyes.

Acid anthraquinone dyes were synthesized by condensation of bromaminic acid with aromatic aminosilanes.

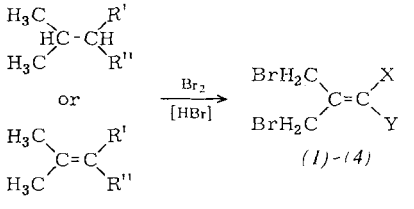
Trimethylsilyl-substituted aromatic amines react with leucoquinizarin to give anthraquinone dispersion dyes. Comparison with *tert*-butyl substituted dyes revealed a distinct superiority of the trimethyl substitution as regards affinity, and stability toward light and chlorine. All the dyes and intermediates investigated showed the typical bands at 750, 835, 1250 cm^{-1} for $-Si(CH_3)_3$ and at 1095 and 1120 cm^{-1} for $-Si(C_6H_5)_3$ in their IR spectra.

Lecture at Erlangen on January 15, 1971 [VB 274 IE]
German version: Angew. Chem. *83*, 258 (1971)

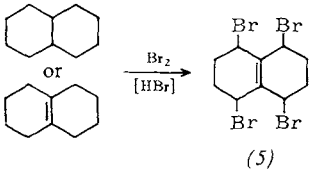
Bromination in Liquid Bromine

By *Hermann Stetter* and *Erhard Tresper*[*]

The bromination of adamantane in liquid bromine has already been shown to proceed *via* an ionic mechanism that leads to a stepwise selective bromination of the tertiary hydrogen atoms. It has also been shown that defined bromination products can be obtained, sometimes in high yields, on bromination of aliphatic hydrocarbons with adjacent tertiary carbon atoms and in the case of tetraalkylated ethylenes. The reactions carried out may be summarized as follows:



(1)-(4)



(5)

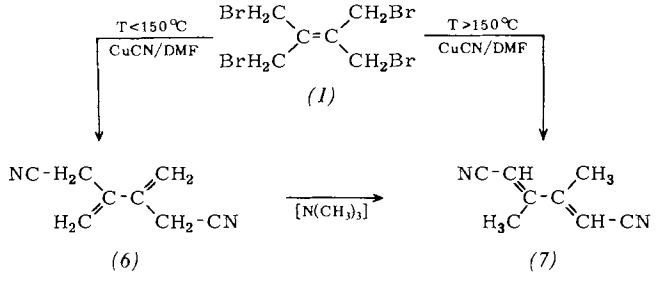
	R'	R''	X	Y
(1)	CH_3	CH_3	CH_2Br	CH_2Br
(2)	C_2H_5	CH_3	$CHBr—CH_2Br$	CH_2Br
(3)	n-C_3H_7	CH_3	$CHBr—CHBr—CH_3$	CH_2Br
(4)	C_2H_5	C_2H_5	$CHBr—CH_2Br$	$CHBr—CH_2Br$

In studies of the reactivity of the bromination product tetrakis(bromomethyl)ethylene *(1)* in the nitrile syn-

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[*] Prof. Dr. H. Stetter and Dr. E. Tresper
Institut für Organische Chemie der Technischen Hochschule
51 Aachen, Prof.-Pirlet-Strasse 1 (Germany)

thesis, the reaction with cuprous cyanide took the following interesting course:



(1) (6) (7)

A series of characteristic reactions was undertaken with the nitriles *(6)* and *(7)*.

Lecture at Aachen on January 22, 1971 [VB 276 IE]
German version: Angew. Chem. *83*, 296 (1971)

Photochemical *cis-trans* Isomerization of *n*-Octenes in the Presence of Organoaluminum Compounds

By *Siegfried Warwel, Heinz-Peter Hemmerich*, and *Friedrich Asinger*[*]

Pure *cis-trans* isomerization of an olefin can be effected by reversible radical addition at the olefinic double bond or *via* a photochemical route using UV light or γ-radiation; in the latter cases the presence of photosensitizers such as benzene or benzophenone is usually necessary.

We have now found that *n*-octenes containing an internal double bond also undergo *cis-trans* isomerization when subjected to irradiation with UV light or γ-rays if molar amounts of an organoaluminum compound ($HAlR_2$[1] or AlR_3) are present. This *cis-trans* isomerization, which under otherwise similar reaction conditions is not observed in the absence of the organometallic compound, proceeds without any shift of the CC double bond in the olefin molecule and leads, irrespective of the configuration of the olefin used, almost to the thermodynamically stable equilibrium mixture of the configurational isomers. Thus, *e.g.*, γ-irradiation (^{60}Co source, dose: 4.3×10^6 rad) of *cis-n*-4-octene for 37 h in presence of tri-*n*-butylaluminum (molar ratio 1:4) at 22 °C leads to an *n*-4-octene which consists of only 17.8% *cis*-, but 82.2% *trans-n*-octene. On irradiation of *trans-n*-4-octene the product of the isomerization reaction contained *cis* and *trans* isomers in the ratio 18.1:81.9.

Not only $Al(n\text{-}C_4H_9)_3$, but also $HAl(i\text{-}C_4H_9)_2$, $Al(i\text{-}C_4H_9)_3$, and $Al(n\text{-}C_8H_{17})_3$ effect a pure *cis-trans* isomerization; the extent of isomerization differs in each case, $Al(n\text{-}C_8H_{17})_3$ being considerably less effective than the other compounds.

The configurational isomerization is noticeably hindered if the organometal compound is complexed by electron donors. Triethylamine, tetrahydrofuran, and di-*n*-butyl sulfide hinder the isomerization almost completely. The mechanism of the isomerization reaction is as yet unknown, but it most probably involves the participation of metal-olefin π complexes as active intermediates.

Lecture at Aachen on January 22, 1971 [VB 275 IE]
German version: Angew. Chem. *83*, 296 (1971)

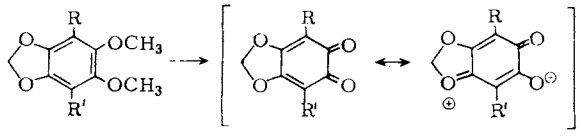
[1] *S. Warwel* and *H.-P. Hemmerich*, Tetrahedron Lett. *1970*, 3185.

[*] Dr. S. Warwel, Dipl.-Chem. H.-P. Hemmerich, and Prof. Dr. F. Asinger
Institut für Technische Chemie und Petrolchemie der Technischen Hochschule
51 Aachen, Alte Maastrichter Str. 2

Substituted *o*-Benzoquinones[1]

By *Franz Dallacker, Zoltan Damó*, and *Gernot Löhnert*[*]

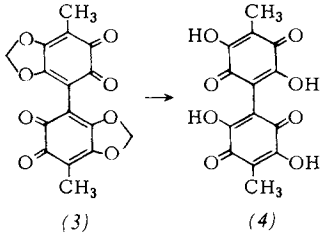
We have synthesized low molecular secondary plant substances by treating the compounds *(1a)–(1c)*, which are readily prepared by reaction of alkyl halides with 2,3-dimethoxy-5,6-methylenedioxyphenyllithium, with dilute nitric acid. Resonance stabilized 4,5-methylenedioxy-*o*-benzoquinones *(2a)–(2c)* are formed in good yields.



(1) (2)

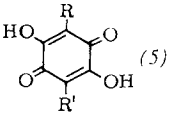
R	R'	(1) M. p. (°C)	(1) Yield (%)	(2) M. p. (°C)	(2) Yield (%)
(a) $H_3C-(CH_2)_{10}$	H	43	72	110–111	74
(b) $H_3C-(CH_2)_{12}$	H	49–50	69	105–107	78
(c) $H_3C-(CH_2)_{18}$	H_3C	49–50	65	114	75

The ditoluene-di-*o*-quinone derivative *(3)* (dec. pt. 256 °C) can be prepared in 72% yield by the same method.



(3) (4)

When aqueous potassium hydroxide solutions of the quinones *(2a)–(2c)* and *(3)* (if necessary with addition of a few milliliters of ethanol) are acidified with hydrochloric acid, the natural substances embelin *(5a)*, rapanon *(5b)*, oosporein *(4)*, and the dehydromaesaquinone *(5c)* are precipitated in high yields.



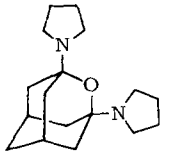
(5)

Lecture at Aachen on January 22, 1971 [VB 277 IE]
German version: Angew. Chem. *83*, 297 (1971)

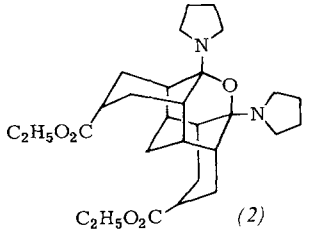
[*] Prof. Dr. F. Dallacker, Dr. Z. Damó, and Dipl.-Chem. G. Löhnert
Institut für Organische Chemie der Technischen Hochschule
51 Aachen, Prof.-Pirle-Str. 1

[1] Derivatives of Methylenedioxybenzene, Part 29.—Part 28: *F. Dallacker*, Monatsh. Chem. *100*, 742 (1969).

Preparation of larger sections of diamond-type lattice has been attempted by *H. Stetter* and *K. Komorowski*. Bicyclo-[3.3.1]nonan-3,7-dione is allowed to react with pyrrolidine to give the 2-oxaadamantane derivative *(1)*, which loses water and is converted into the bisenamine 3,7-dipyrrolidinobicyclo[3.3.1]nona-2,7-diene. Reaction of this bis-



(1)



(2)

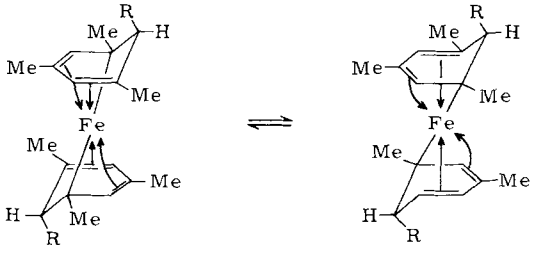
enamine with ethyl α-bromomethylacrylate affords the pentacycle *(2)*. / Chem. Ber. *104*, 75 (1971) / –Ee.

[Rd 312 IE]

The electron-induced topotactic decomposition reactions of SnS_2 and $Cu(OH)_2$ have been investigated by *J. R. Günter* and *H. R. Oswald*. The electron diffraction diagrams of thin lamellas of SnS_2 (CdI_2 type) show, even after short irradiation, reflections of elementary tin, which is present in three crystallographically equivalent orientations to the SnS_2. Holes are formed at the same time. The (001) layer is the structure-retaining element.—The thermal decomposition of SnS_2 follows a completely different course: it leads, *via* the intermediary Sn_2S_3, to formation of SnS. In the case of $Cu(OH)_2$ (chain structure) very small CuO crystals can be detected after a short irradiation time whose [110] axes are parallel to each other and to the [100] axis of $Cu(OH)_2$, but tilted. Further irradiation leads to formation of small crystals of Cu_2O. The structure is retained in the [100] chain. The majority of such reactions are controlled two-dimensionally or unidimensionally; in topotactic reactions the compounds taking part do not necessarily have to have related structures. / Chimia *24*, 421 (1970) / –Kr.

[Rd 313 IE]

Pseudoferrocenes have been studied by *J. F. Helling* and *D. M. Braitsch*. Bis(6-*tert*-butyl-1,3,5-trimethylcyclohexadienyl)iron(II) *(1)* and the phenyl analog *(2)* prepared by reaction of bis(mesitylene)iron(II)hexafluorophosphate with *tert*-butyl or phenyllithium show temperature-dependent, simple NMR spectra indicative of fluxional behavior. The spectra allow either free rotation with respect to the ring-Fe-ring axis or lack of rotation but do not permit hindered



(1), R = $C(CH_3)_3$
(2), R = C_6H_5

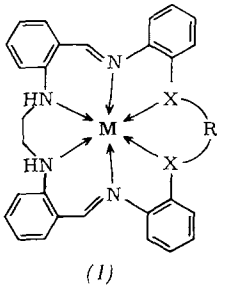
rotation. *(1)* and *(2)*, m.p. 203–204 °C and 102–105 °C respectively, are stable toward air and water. At and above the temperature at which the high temperature limiting NMR spectra are found (+100 and +2 °C resp.), *(1)* and *(2)* are possibly present as homocyclopentadienide ion complexes, *i.e.* as "pseudoferrocenes". / J. Amer. Chem. Soc. *92*, 7207, 7209 (1970) / –Kr.

[Rd 314 IE]

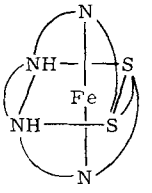
Hydridobis(π-cyclopentadienyl)phenyltungsten $(\pi\text{-}C_5H_5)_2WHC_6H_5$ has been prepared by *M. L. H. Green* and *P. J. Knowles* by reaction of dihydridobis(π-cyclopentadienyl)tungsten with benzene in the presence of dienes such as isoprene at 120 °C. The yellow, sublimable phenyl derivative is formed in 15% yield. If toluene is used instead of benzene only the *p*-derivative is formed. A similar addition of benzene has been postulated to occur in H/D exchange reactions of C_6D_6 with H_2 that are catalyzed by $(\pi\text{-}C_5H_5)_2TaH_3$. / Chem. Commun. *1970*, 1677 / –Ee.

[Rd 317 IE]

Metal complexes of new macrocyclic sexadentate ligands have been investigated by *P. A. Täsker* and *E. B. Fleischer*. Complexes such as *(1)* were prepared *in situ* from 2,2'-(ethylenediamino)dibenzaldehyde, the perchlorate of the desired metal (Fe^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}) and a diamine containing two additional donor sites. X-ray structure ana-



(1)

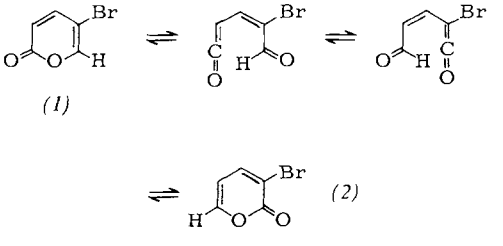


(2)

lysis of *(1)*, M = Fe, X—R—X = S—CH_2—CH_2—S, showed that all six donor atoms are arranged octahedrally about the central iron atom as in *(2)*. / J. Amer. Chem. Soc. *92*, 7072 (1970) / –Ee.

[Rd 315 IE]

Skeletal rearrangement with participation of 1,5-sigmatropic hydrogen shifts is reported by *W. H. Pirkle, H. Seto*, and *W. V. Turner* to be the underlying rearrangement *via* which the already well-known methyl migration occurs in the pyrolytic decarboxylation of 5-methyl-6-carboxy-2-pyrone to 3-methyl-2-pyrone and related reactions. To test



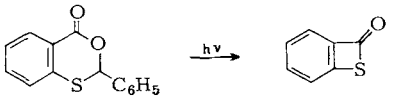
(1)

(2)

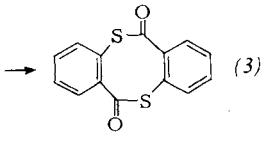
this hypothesis the authors pyrolyzed 5-bromo-2-pyrone *(1)* and found that the recovered material consisted of an approximately 50:50 mixture of 3-bromo-2-pyrone *(2)* and *(1)*. The postulated occurrence of ketene aldehydes as intermediates was supported by the low-temperature IR spectroscopic detection of the unsubstituted analog in the photolysis of 2-pyrone. / J. Amer. Chem. Soc. *92*, 6984 (1970) / –Ee.

[Rd 316 IE]

2-Thiobenzopropiolactone *(2)*, the thio analog of the unknown benzopropiolactone, has been synthesized by *O. L. Chapman* and *C. L. McIntosh* by irradiation of the



(1) *(2)*



(3)

benzoxothianone *(1)* at –196 °C in $CHCl_3$; presence of the new species was confirmed by IR spectroscopy (ν(C=O) = 1803 cm^{-1}). Warming of the irradiated sample to –40 °C gives rise to formation of the dimer *(3)* from *(2)*. When the irradiation of *(2)* is carried out in the presence of methanol methyl *o*-mercaptobenzoate is formed. / J. Amer. Chem. Soc. *92*, 7001 (1970) / –Ma.

[Rd 318 IE]

A new method for the synthesis of *N*-oxides of polyhalogenated N-hetero aromatics is described by *G. E. Chivers* and *H. Suschitzky*. It involves oxidation with a mixture of concentrated sulfuric acid, H_2O_2, and acetic or trifluoroacetic acid. The principle of the reaction is nucleophilic attack of the amino nitrogen on the peroxide oxygen whose electrophilic character is enhanced by protonation of the peracid that is formed as intermediate. Examples: *N*-oxide from pentachloropyridine, 85% yield; 2,3,5,6-tetrachloropyridine, 80%; 2,6-dichloropyridine, 65%; 2,3,5,6-tetrachloro-4-nitropyridine, 67%; 2,3,5,6-tetrachloro-4-methylpyridine, 70%; pentabromopyridine, 85%; tetrachloropyrazine, 56%; tetrachloropyridazine, 50%. / Chem. Commun. *1971*, 28 / –Ma.

[Rd 319 IE]

The molecular structure of tetrasulfur dinitride (1,2,3,5,4,6-trithiathia$^{(IV)}$diazine) has been investigated by *J. Nelson* and *H. G. Heal*. After preparation by two methods and purification by chromatography and sublimation S_4N_2 proved to be a single substance. Its dipole moment is 1.74 ± 0.28 D; it was determined *via* the dielectric constants and refractive indices of CS_2 solutions. The ^{14}N-NMR spectrum shows a single resonance at 105 ± 1 ppm upfield from aqueous nitrate ion. The mass spectrum at low ionizing voltage contains only a signal for $S_4N_2^+$, thus establishing



(1)

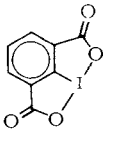
the molecular weight. The electronic spectrum shows three bands at 220, 377, and about 455 nm; the last one is ascribed to the n→π* transition owing to its solvent dependence. In addition, IR and Raman spectra were measured. The combination of all these physical data leads to *(1)* as the most probable structure among about 60 covalent formulas taken into consideration. At the present stage, however, no distinction is possible between planar, chair, or boat conformations of *(1)*. / J. Chem. Soc. *A 1971*, 136 / –Hz.

[Rd 320 IE]

The adsorption of hydrogen halides on alkali-metal halides has been studied by *R. StC. Smart* and *N. Sheppard* by means of IR spectroscopy. Films of alkali-metal halides with high surface areas (around 200 m^2g^{-1}) were obtained by deposition from the vapor phase on cold (80 °K) carrier surfaces. The dominant surface species is most probably X—H··Y$^-$ (X, Y = halogen) with a hydrogen bond to a surface anion. In favorable cases it was possible to detect all of the three vibrational frequencies of this species; *e.g.*, for HCl on CsCl, 2110, 1160, and 218 cm^{-1}. The strength of the hydrogen bonds of HCl increases along the sequences LiCl < NaCl < CsCl and NaI < NaBr < NaCl. In mixed-halogen systems, halogen exchange is observed if X of HX has a higher atomic number than Y of the salt. / Proc. Roy. Soc. (London) *A 320*, 417 (1971) / –Hz.

[Rd 321 IE]

The ^{127}I Mössbauer spectra of aromatic compounds with polyvalent iodine have been investigated by *B. S. Ehrlich* and *M. Kaplan*. ZnTe with ^{127m}Te was used as the source for the 57.6 keV transition of ^{127}I; source and absorber were cooled to 4.2 °K. The compounds investigated were iodobenzene PhI, iodobenzene dichloride $PhICl_2$, iodosobenzene PhIO, iodoxybenzene $PhIO_2$, and the di-"lactone" of 2-iodoisophthalic acid *(1)*. The analysis of the quadru-

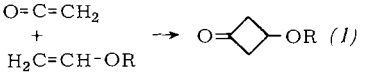


(1)

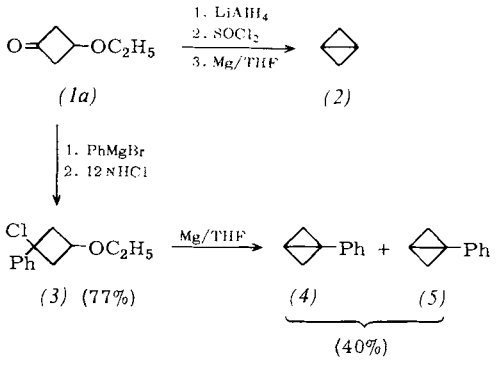
pole splitting, asymmetry parameter, and isomer shift revealed that in all compounds, with the exception of $PhIO_2$, only p orbitals of iodine participate in bonding. Accordingly, the C—I—O angle in PhIO is about 90°; compound *(1)* is approximately planar with a linear O—I—O group. In $PhIO_2$ the bonding orbitals show slight s hybridization; the angle O—I—O is predicted to be about 95°. / J. Chem. Phys. *54*, 612 (1971) / –Hz.

[Rd 322 IE]

3-Alkoxycyclobutanones *(1)*, **precursors of bicyclo[1.1.0]-butanes,** have been prepared by *J. B. Sieja* by addition of ketene to vinyl ethers at 100 °C:



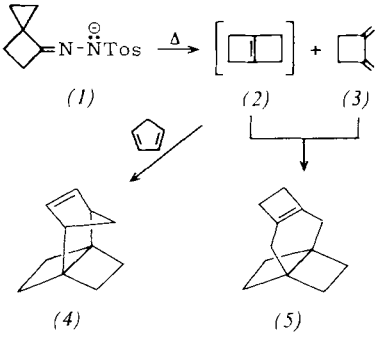
The reactivity decreases along the series R = *tert*-butyl ≫ ethyl > methyl > benzyl (yield 20–87%). The 3-alkoxycyclobutanones serve as starting materials for many bicyclobutanes. The parent compond *(2)* is formed *via* the alcohol



(87%) and the chloride (70%) in 70% yield. 1-Phenyl *(4)*, 1-vinyl, and 1-cyano derivatives can be prepared similarly./ J. Amer. Chem. Soc. *93*, 130 (1971) / –Ma.

[Rd 323 IE]

The synthesis of bicyclo [2.2.0]hex-1(4)-ene *(2)*, from which the theoretically interesting hydrocarbons tricyclo-



[2.2.1.$0^{1,4}$]heptane and tricyclo[2.2.2.$0^{1,4}$]octane may prove preparable, has been described for the first time by *K. B. Wiberg*, *G. J. Burgmaier*, and *P. Warner*. Thermolysis of the Na salt of spiro[2.3]hexanone 4-tosylhydrazone *(1)* in a high vacuum [the volatile products being trapped in liquid nitrogen which is then allowed to evaporate at room temperature] yields 1,2-dimethylenecyclobutane *(3)* and the dimer *(5)*, which can be regarded as a Diels-Alder adduct of *(2)* and *(3)*. Compound *(2)* could be detected in the thermolysis products of *(1)* by addition of cyclopentadiene to the liquid nitrogen. The adduct *(4)* was formed on heating to room temperature. / J. Amer. Chem. Soc. *93*, 246 (1971) / –Ma.

[Rd 324 IE]

Reactions of silicon difluoride with silanes and germanes have been studied by *J. L. Margrave*, *D. L. Williams*, and *P. W. Wilson*. These authors mixed gaseous SiF_2, prepared from SiF_4 and Si, with the relevant silane or germane in a flow system and subsequently condensed the gases as fast as possible at –196 °C. The volatile products were isolated after warming to room temperature. Under these conditions, SiF_2 does not react with $Si(CH_3)_4$ or $Ge(CH_3)_4$; with $Si(CH_3)_3Cl$ it forms $Si(CH_3)_3F$, presumably by halogen exchange. In contrast SiF_2 and $Si(CH_3)_3OCH_3$ react *via* insertion into the Si—O bond to give $Si(CH_3)_3F$, $(CH_3)_3Si—Si(CH_3)_2F$, CH_3OSiF_3, and a little $(CH_3)_3Si—SiF_3$. The initial product is probably $(CH_3)_3Si—SiF_2OCH_3$. Insertion into the CH_3—O bond is somewhat less likely. / Inorg. Nucl. Chem. Lett. *7*, 103 (1971) / –Ee.

[Rd 326 IE]

A new mercury ion, Hg_3^{2+}, has been detected by *G. Torsi* and *G. Mamantov* in acidic $NaCl/AlCl_3$ melts containing $HgCl_2$ or Hg_2Cl_2 to which metallic mercury had been added. Hg_3^{2+}, which renders the solution yellow, exhibits an asymmetric absorption band with $\lambda_{max} = 325$ nm. The ion can also be obtained by polarographic reduction of Hg^{2+} in acidic $NaCl/AlCl_3$ melts. Further indications of its existence have been afforded by the reactions of $HgCl_2$ or Hg_2Cl_2 with Hg in pure $AlCl_3$ melts. / Inorg. Nucl. Chem. Lett. *6*, 843 (1970) / –Kr.

[Rd 299 IE]

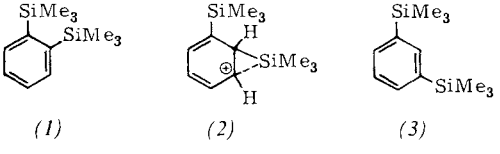
Alkyl nitrates can be prepared by deamination of primary amines with N_2O_4, according to *F. Wudl* and *T. B. K. Lee*. The reaction is strongly dependent on the solvent. It proceeds most satisfactorily at low temperature (*ca.* –60 °C) in THF and other ethers, which, as Lewis bases, can form strong complexes with N_2O_4:

$$R—NH_2 + N_2O_4 \xrightarrow[-60\,°C]{THF} R—ONO_2 + N_2 + H_2O$$

Examples: $R = CH_3(CH_2)_3CH(C_2H_5)CH_2$, 65% yield; $C_6H_5CH(CH_3)$ 80%; $CH_3(CH_2)_5$, 20%. Extensive retention of configuration indicates an ionic mechanism./J. Amer. Chem. Soc. *93*, 271 (1971) / –Ma.

[Rd 325 IE]

A new organosilicon rearrangement has been discovered by *D. Seyferth* and *D. L. White*. On reaction for 48 h in the presence of benzene and trifluoroacetic acid at 150 °C in mixture of *(1)* (2%), the *meta* isomer *(3)* (93%), and the *para* isomer (5%), alongside a small amount of trimethyl-



phenylsilane. The *meta* and *para* isomers undergo only very slight rearrangement under the same conditions. In the absence of trifluoroacetic acid all three isomers are stable. The authors assume that the rearramgement is similar to the 1,2-shift in dialkylbenzenes *via* intermediates such as *(2)*, which has been described by Olah[1]./J. Organometal. Chem. *26*, C15 (1971)/-Ee.

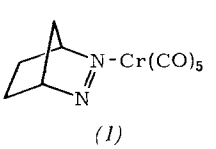
[Rd 327 IE]

[1] *G. A. Olah et al.*, J. Org. Chem. *29*, 2310, 2313, 2315, 2687 (1964).

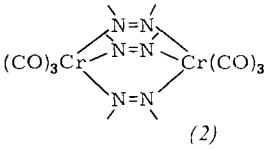
Coordination compounds of 2,3-diazabicyclo[2.2.1]hept-2-ene have been prepared by *M. Herberthold* and *W. Golla*. The ligand gives three types of complex with carbonyl: metals: 1) In *(1)* [obtained from the bicyclic and photolyti-

cally produced $Cr(CO)_5$] it functions as a unidentate two-electron ligand. 2) In *(2)* [formed on heating of *(1)*] the bicyclic behaves like a bidentate four-electron ligand (although a structure having only one azo bridge and two chelating ligands cannot be dismissed altogether). 3) The bicyclic reacts with $Fe_2(CO)_9$ to give *(3)* in which the azo group can be formally regarded as a six-electron ligand. *(1)* to *(3)* and some similar compounds can be sublimed in high vacuum and are fairly stable toward air./J. Organometal. Chem. *26*, C27 (1971)/-Kr.

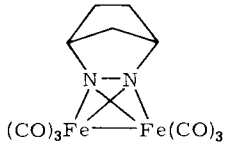
[Rd 328 IE]



(1)



(2)



(3)

BOOK REVIEWS

Chemische Spektralanalyse (Seith–Ruthardt), Anleitung für die chemische Laboratoriumspraxis (Chemical Spectral Analysis, Introduction to Chemical Laboratory Practice) Vol. 1. By *W. Rollwagen*. Springer Verlag, Berlin-Heidelberg-New York 1970. 6th ed., xii, 185 pp., 84 Figs, and 1 Table, bound DM 48.—.

"Chemische Spektralanalyse" has for some decades been the most important German-language introduction to practical emission-spectral analysis. The fundamental principles formulated by *Seith* and *Ruthard* in their description of sample preparation, light sources, light conduction, spectral breakdown, radiation receivers, and particularly evaluation still deserve the attention of all those who wish to use emission-spectrochemical methods of analysis. *Rollwagen*, who revised and expanded the 5th edition (1959), has also made some additions in the present 6th edition. The section on photoelectric measurement has been expanded. The determination of gases in metals and calibration by the addition method are discussed. The new section on *Grimm*'s glow discharge lamp must obviously have been inserted at a time when knowledge of this interesting and important light source was inadequate. There are many instances where failure to revise the text is regrettable: this is so *e.g.* wherever a qualitative description is given for some point that could nowadays be presented more easily by means of a simple formula. The required slit width and systematic focusing steps are easier to calculate from the data for the spectral apparatus than to find by trial and error. These and other formulas are nowadays tools that should not be lacking from this book, which contains so much important information.

Hans Massmann [NB 950 IE]

The Chemistry of Inorganic Ring Systems, Parts 1 and 2. By *I. Haiduc*. John Wiley and Sons Ltd., New York 1970. 1st ed., vi, 1197 pp., £10.00.

In 1960, *Ionel Haiduc* wrote a remarkable book in Romanian on inorganic ring systems. He now spotlights this fascinating and fast-developing field of inorganic chemistry once again in a much more comprehensive work in English. The work is divided into two parts. The first deals with homocyclic inorganic ring systems and with heterocycles whose main component is an element of group III or IV. The second part covers heterocycles whose main component is an element of group V or VI and heterocycles that are coordination compounds containing metals. Since the assignment of the individual heterocycles to these groups cannot always be free from arbitrary choice, a good keyword index is helpful in finding one's way around. A list of contents precedes each chapter.

The work contains an abundance of material. The recent literature is taken into account. The literature coverage is admittedly not complete, and probably was not intended to be so; however, the selection is excellent. All the important inorganic ring systems and their principal chemical and physical properties are surveyed. The discussion of chemical behavior includes substitutions that proceed with retention of the ring system, together with their problems, as well as reactions in which the ring system is opened. The physical properties are collected in tables in many cases. The emphasis is always placed on the phenomenological. Mechanistic aspects are mentioned only briefly. In this way the reader is acquainted with the most important substances and their behavior. At the same time he is directed by numerous references (about 5000) to the original literature, from which he can obtain further information. It is felt, however, that the chapters on structure and bonding in inorganic rings and on inorganic ring systems in equilibrium might have been rather more detailed. The chapter on bonding theory contents itself with a superficial indication of the problems. The very stimulating chapter on inorganic rings in equilibrium, which was written by the author at the suggestion of and with the aid of *J.R. Van Wazer*, should have presented more qualitative description.

To summarize, it can be stated that this is an outstanding work offering an excellent introduction to the field of inorganic heterocycles, and showing how fluid the boundaries between inorganic and organic chemistry have now become. The inorganic heterocycles lie at a particularly interesting junction between these regions. The book, which is clearly and simply written, can be strongly recommended to chemists interested in this field as well as to students.

Margot Becke [NB 955 IE]

13. MAI 1971

Surfactant Biodegradation, Surfactant Science Series, Vol. 3. By *R. D. Swisher*. Marcel Dekker Inc., New York 1970. xxiii, 496 pp. bound $ 33.50.

The author, who is well known in the field of surfactant research, has undertaken the task of sorting through the vast literature on the biological degradation of surfactants and presenting its substance in the form of a monograph. He summarizes present-day knowledge in eight chapters. He first describes the introduction of the alkylbenzenesulfonates around 1950 and their first effects on water management, particularly on clarifying plants and rivers; general remarks on biological degradation pathways are also included. Then follow data on the physical and chemical properties and on the structures of anionic and nonionic surfactants. A long chapter is then devoted to the analysis of surfactants, which is difficult from the very point of view with which the book is concerned, *i.e.* the degradation of surfactants in very low concentrations. The author concentrates on the methylene blue method for anionic surfactants, while several methods are discussed for nonionic surfactants. Special physicochemical methods also allow an insight into the detailed structures and their modification during degradation.

Nonspecific methods based on measurement of the biological oxygen requirement or of the interfacial tension are also mentioned briefly. The microbiological questions of surfactant degradation are carefully discussed before a long chapter is devoted to the microbiological degradation test methods; practically all the methods used in laboratories and in practice are discussed here. The interactions between surfactant structure and microbial attack are then presented. Finally, existing knowledge about the metabolic pathways in the total degradation of surfactants is discussed. Tables covering 83 pages present the results reported by many research workers, showing surfactant structure, time, and analytical method. The work is completed by a 56 page bibliography and a 27 page subject index. It should be an important tool to all those who are concerned with surfactants, particularly their effect on water management.

K. J. Bock [NB 948 IE]

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Synthetic Paper

By Hans Lunk and Karl Stange[*]

Synthetic paper can be made either by forming a web from synthetic fibers or by extruding a film from thermoplastic polymers. With suitable starting materials and appropriate treatment it is possible to equal the properties of conventional cellulose paper; in some respects, as in wet strength and dimensional stability, the synthetic papers are clearly superior.

1. Introduction

Since the beginning of the 19th Century, the 2000-year-old craft of papermaking has developed into a highly technological industry with a world-wide production of over 120 million tons per year. This tremendous progress was due to the invention and further development of efficient machines for the continuous production of paper. The raw material itself has not changed; as in ancient times, cellulose fibers are still used.

[*] Dr. H. Lunk and Dr. K. Stange
Badische Anilin- & Soda-Fabrik
67 Ludwigshafen (Germany)

In the last few years, however, a development has started which deviates from this tradition: the application of plastics in place of the cellulose fibers. This development is not unusual; other natural products such as textile fibers, wood, and leather have been replaced to a considerable extent by synthetic polymers. In the case of paper, the use of plastics was delayed, partly for technical reasons, but mainly because of the relatively low cost of the conventional raw material and manufacturing process. This article is a description of the present state of development of synthetic paper; methods of preparation, properties, and possible applications will be described.

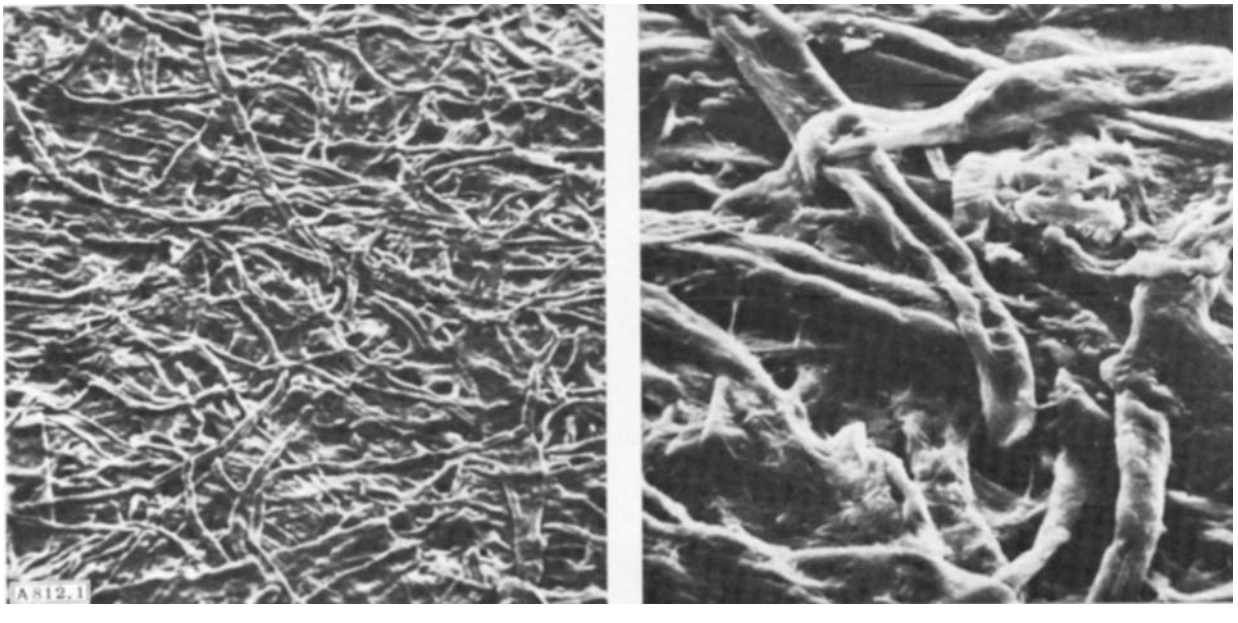


Fig. 1. Surface of a typewriter paper (Stereoscan picture). Enlargement: left, 100:1, right, 500:1.

Before discussing synthetic paper, it may be useful to say a few words about the production and the structure of cellulose paper. Today, paper is almost exclusively made from wood. A suspension of cellulose fibers, obtained from wood chips either by chemical treatment or by mechanical grating (groundwood), is poured onto a continuously moving sieve. Most of the water is removed here, and the resulting sheet is dried on a series of rolls and cylinders. Modern paper machines have working widths of up to 9 meters and speeds of about 600 to 800 meters per minute. The product of these machines is a mat of interlocked cellulose fibers as shown in Fig. 1. By adding fillers and size in the appropriate amounts, one obtains the different types of paper. The surface can then be further improved by application of a pigment coating.

Synthetic papers may be classified into two different types. The first one has a fibrous structure like cellulose paper, with synthetic fibers made from polyamides, polyester, or polyolefins replacing the cellulose fibers. Such synthetic fiber webs have excellent properties, but they are quite expensive because of the high cost of the raw materials. The other type of synthetic paper does not use fibers; rather, a film is directly extruded from a thermoplastic polymer. These products differ considerably in their structure from cellulose paper, and thus present a whole variety of different problems.

2. Paper-like Webs from Synthetic Fibers

2.1. Fabrication *via* the Paper Process

One method of making synthetic paper consists in replacing the cellulose fibers by synthetic fibers cut to the appropriate length. A suspension of such fibers is run through regular paper machines, taking advantage of the high production speed and uniform product thickness achievable with such equipment. The products have essentially the same structure as cellulose paper, and therefore possess good printability and ink absorbing qualities. Because of the different fibers, they also have properties which deviate from those of regular paper. Synthetic fibers generally exhibit lower water absorption than cellulose fibers; the webs made from them are therefore less sensitive to moisture, and possess greater wet strength and dimensional stability. The excellent mechanical properties of the synthetic fibers are reflected in the fiber webs. They have high tensile strength, tear strength, and above all, high folding endurance. Commercial papers made from synthetic fibers are shown in Table 1.

In place of spun fibers, one can also use fibers made in a different way. If olefins are polymerized with certain Ziegler-Natta catalysts under conditions of high shear, the polyolefin is obtained in the form of fine, mattable fibers. These can be used, either by themselves or in combination with other fibers, to make products quite similar to the fiber webs mentioned above[1]. This method is not yet used in practice, but has probably good chances for commercial success because of the relatively low cost.

2.2. Thermally Bonded Fibrous Sheets

Another process for the fabrication of synthetic fiber webs does not involve a suspension of staple fibers, but uses continuous filaments. During the extrusion, the filaments are placed on top of one another in an unordered array and at the same time thermally welded together (spunbonded). Commercially available products made from high density polyethylene, polypropylene, polyester, and polyamide are shown in Table 1 with trade names and producers.

The properties of these sheets are of course largely dependent on the kind of synthetic fiber used. Generally, they are between those of paper and woven fabrics. Since these materials are also intermediate in their prices, they are used as durable paper with especially good mechanical properties and also for disposable textile products.

Table 1. Synthetic fiber webs.

Trade name	Producer	Raw material	Process
Syntosil®	Zürcher Papierfabrik	polyamide	from staple fiber on conventional paper machines
Neobond®	Feldmühle	polyamide	
Tyvek®	DuPont	HD-polyethylene	continuous fibers, thermally bonded
Typar®	DuPont	polypropylene	
Reemay®	DuPont	polyester	
Bidim®	Rhodiaceta	polyester	
Viledon®	Freudenberg	polyamide	

3. Extruded Film

3.1. Fabrication

There are two different extrusion processes for the fabrication of film from thermoplastic materials. In both cases, the polymer is plasticated in the extruder, advanced by a rotating screw, and finally forced through the die.

In the cast film process (Fig. 2) the polymer melt is extruded through a slot die. After extrusion, the film is quenched on a water cooled chill roll and then wound up. The thickness of the film can be varied by adjusting the width of the die slot and the take-off speed. Usually it is necessary to trim the edges in order to obtain the desired width of the film and to remove material with differing film thickness.

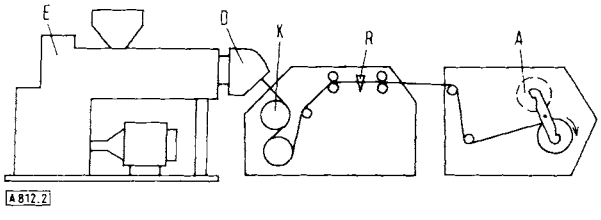


Fig. 2. Cast film process. E = extruder, D = die, K = chill roll, R = edge trimmer, A = windup.

In the blown film process (Fig. 3) the melt is forced through a circular die. The tubing thus formed is blown up to the desired diameter, air cooled for a certain distance, and then laid flat by means of two nip rolls. Both edges are trimmed and the two resulting layers of film are wound up separately.

The main advantage of the blown film process is that through high blow-up ratios relatively thin and broad films can be produced. On the other hand, the maintenance

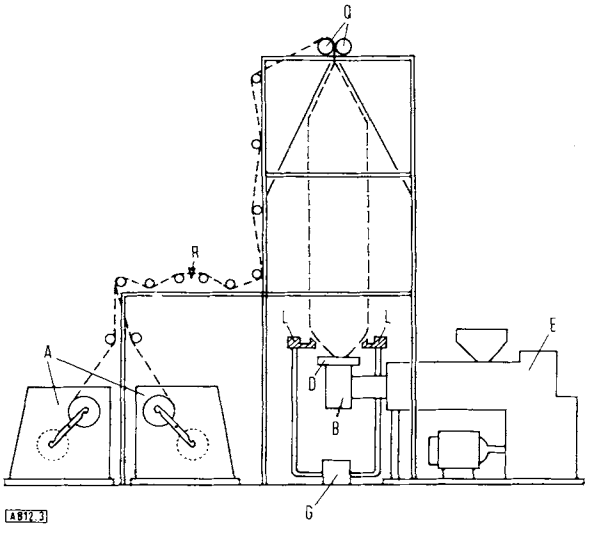


Fig. 3. Blown film process. E = extruder, B = blow head, D = die, L = air cooling ring, Q = nip rolls, R = edge trimmer, A = windup.

of constant thickness over the whole width of the film is somewhat problematic. Depending on the starting material and the intended application, both cast film and blown film processes are used in practice.

A variant of the blown film process is the extrusion of foamed film. Through the addition of blowing agents (usually low boiling hydrocarbons) it is possible to produce foamed film from a variety of polymers. Because of their special properties (thermal insulation and shock absorption) they are a valuable addition to the compact films.

3.2. Stretching

Frequently it is desirable to improve the mechanical properties of the film by stretching. By application of external forces the chain molecules can be oriented in such a way that the chain axes lie preferentially in the plane of the film. As a result, tensile strength, tear strength, stiffness, as well as some other properties are improved. Since it is desirable that the properties be equal in all directions of the plane of the film, the stretching has to be done biaxially, *i.e.* in two directions at right angles to each other. The stretching is usually carried out at a temperature in the thermoplastic region above the glass point, with crystalline polymers between glass point and melting point. It is important, especially with amorphous polymers, to freeze the orientation of the molecules by rapid quenching. The stretch ratio depends on the material and on the properties desired; usually it is between 2:1 and 4:1 in both directions, and for crystalline polymers frequently somewhat higher.

Two methods are used for the biaxial stretching of cast film: the simultaneous stretching process, in which the stretching is carried out in both directions at the same time, and the two-stage process, in which the two stretching operations are carried out consecutively. Fig. 4 illustrates the principle of a simultaneous stretching machine and the deformation of a unit element during the stretching process. As it comes from the extruder, the film is gripped by special clamps on two continuous chains. In the stretching zone, the two chains move away from each other, and at the same time the distance between the individual clamps is increased, resulting in a biaxial stretching of the film.

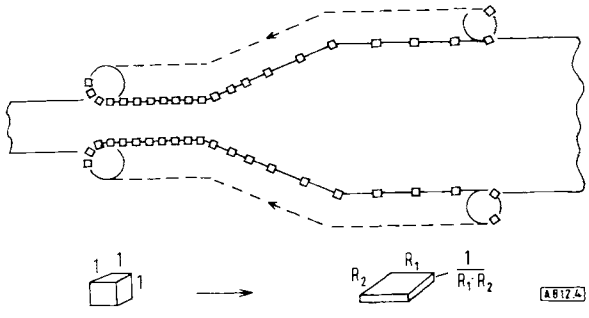


Fig. 4. Machine for simultaneous biaxial stretching of film. R_1 = stretch ratio "along", R_2 = stretch ratio "across".

The two-stage stretching unit is shown in Fig. 5. First, the film is stretched lengthwise on a series of rolls with increasing speed, then across in the second part of the machine. As in the simultaneous process, the film is gripped by two continuously moving chains with clamps. In the stretching zone, the chains move apart; the distance between the clamps, however, stays constant.

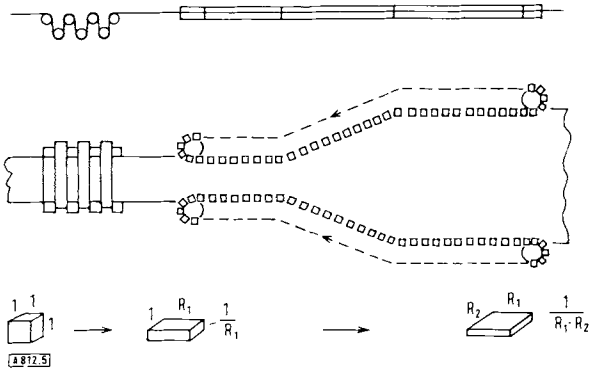


Fig. 5. Two-stage film stretching unit. R_1 = stretch ratio "along", R_2 = stretch ratio "across".

Apart from these methods of stretching cast film, there are also a number of methods for stretching blown film. Although it is possible to stretch blown film during extrusion and blow-up, the orientation achievable in the transverse direction is usually insufficient. The patent literature describes several procedures in which tubular film is stretched by blowing it up again after it has passed the nip rolls[3].

The process of stretching is expensive in each of the described variations. However, it improves the properties of the materials to such an extent that thinner films or less expensive raw materials can be used. Although the oriented film is weakened along a line perpendicular to its plane, this is not much of a disadvantage since the mechanical demands in this direction are rather small.

3.3. Properties

The differences in the mechanical behavior of cellulose paper and polymer films can best be seen in a stress/strain diagram (Fig. 6). Paper has a relatively low elongation at break, but a high tensile strength. The modulus of elasticity is also high, as can be seen from the slope of the stress/strain curve. Most papers have somewhat different properties in the machine direction (the direction in which the paper moves on the machine during fabrication) and in the cross direction. This difference arises from the preferred orientation of the cellulose fibers in the machine direction, which raises both tensile strength and tensile modulus as shown in Fig. 6.

Polymer films behave somewhat differently in the tensile test. After reaching a certain stress, the tensile yield stress σ_y, a plastic deformation takes place which is not recovered at room temperature. The tensile strength is frequently higher than the yield strength, but for comparison with paper the important property is the yield strength. Beyond it the film becomes permanently deformed, an intolerable condition for most applications. For the same reason, the relatively high elongation at break of the polymer films is of little use.

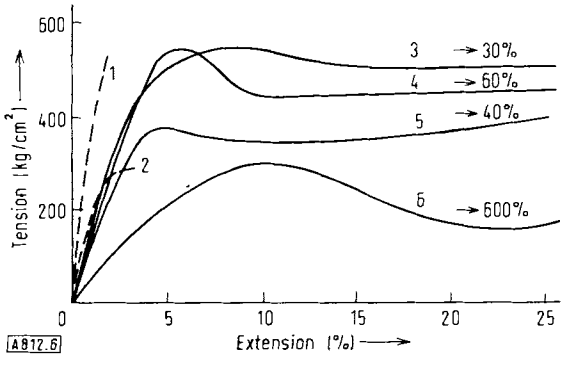


Fig. 6. Stress/strain diagrams of paper and polymer films: 1, paper (along); 2, paper (across); 3, high impact polystyrene (biaxially oriented); 4, polyvinyl chloride; 5, high impact polystyrene; 6, high density polyethylene.

Table 2 summarizes the important mechanical properties of those polymer films which are candidates for the preparation of synthetic paper. For comparison, two cellulose papers are included in this table. In spite of the structural differences between paper and extruded polymer film, the mechanical properties with the exception of the elongation at break are quite similar. It can also be seen that tensile strength and modulus of elasticity are improved considerably by biaxial stretching.

Table 2. Properties of extruded polymer film and cellulose paper.

	Density (g/cm^3)	Yield strength (kg/cm^2) DIN 53455	Elongation at break (%) DIN 53455	Young's modulus (kg/cm^2) DIN 53457	Tear strength (kg/mm) DIN 53363
Unoriented film					
High impact polystyrene	1.05	370	40	24000	1.3
High density polyethylene	0.95	300	600	10000	27
Polypropylene	0.90	320	650	12000	35
Polyvinyl chloride	1.41	550	60	25000	13
Biaxially oriented film					
General purpose polystyrene	1.05	720	6	35000	1.8
High impact polystyrene	1.05	500	30	30000	2.4
Polypropylene	0.90	1000	65	30000	2.3
Polyvinyl chloride	1.41	900	50	34000	2.0
Cellulose paper					
Writing paper, 60 g/m^2 MD/CD [a]	0.80	590, 270	2/4	98000/41000	2.0/2.7
Art paper, 120 g/m^2 MD/CD [a]	1.29	540/270	2/4	74000/42000	2.5/3.0

[a] MD = machine direction, CD = cross direction.

In contrast to cellulose paper, the polymer films are thermoplastic. They deform at elevated temperatures, especially if frozen-in stresses such as those present in stretched films provide a driving force for the deformation. This limits the applications involving high temperatures such as in copying machines. Upper service temperatures for the films listed in Table 2 range from 75 °C (polyvinyl chloride) to 120 °C (polypropylene). An advantage of the thermoplastic behavior is the possibility of melt sealing. By application of heat and pressure, films of the same or of different materials can be permanently bonded together.

With the exception of polyvinyl chloride, the thermoplastics in Table 2 are non-polar. They all have low water absorption, and do not change their properties in the presence of water. Because of the low water absorption, films made from these materials have a high dimensional stability. Depending on the moisture content of the air, cellulose paper absorbs varying amounts of water, which causes dimensional changes of up to two percent. This can be very problematic with multicolor printing, and with tracing paper. It is therefore necessary to store paper at a carefully controlled temperature and humidity if it is to be used for these applications. With films made from the above polymers this problem does not exist.

A disadvantage of the non-polar films is their tendency to acquire static charges, which can lead to difficulties in the printing process when the sheets are fed into the press. This can be overcome by adding suitable polar compounds of low molecular weight, or by post-treatment of the film, *e.g.* by application of a pigment coating. Fig. 7 shows the disappearance of electrostatic charges on films of high impact polystyrene (untreated, with antistatic additive,

and pigment coated). With the latter two, the charge quickly disappears; in this respect they resemble coated paper.

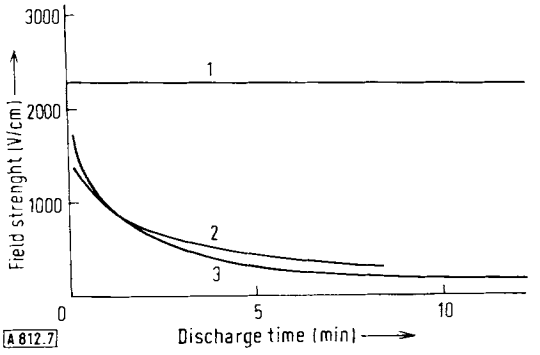


Fig. 7. Disappearance of electrostatic charges on polystyrene films: 1, high impact polystyrene; 2, high impact polystyrene with pigment coating; 3, high impact polystyrene with antistatic additive.

The optical properties of the polymer film depend on the raw material, the additives (*e.g.* pigments), and the fabricating conditions. With most thermoplastic films there are rather wide limits in which opacity, smoothness, and gloss can be adjusted. In contrast to paper, which frequently has a cloudy structure, the films can be made homogeneous. They are therefore better suited for the various photographic processes, provided they can stand the required temperatures.

3.4. Printing

Conventional printing inks and printing processes have been specially developed for paper since it has hitherto been the only printing substrate of significance. The synthetic fiber webs described in the first part of this article are very similar to paper in their structure, and it is generally possible to print or write on them by the usual methods. Not so with extruded films. These have a smooth surface which depends more on the state of the chill rolls than on the material itself. There are no cavities with capillary activity such as between the fibers of cellulose paper or synthetic fiber webs. This combination of smooth surface, low absorbing power, and non-polar structure frequently makes it difficult to print on polymer films: drying times are long, and the adhesion of the printing ink is poor.

In principle, these problems can be approached in two different ways. One can develop special printing inks for the polymer films, or one can treat the surface of the films to make it more receptive. The nature of the polymer as well as the selected printing process will determine which of the two approaches is more appropriate.

Commercial printing methods may be divided into two groups according to the printing inks used. The first group, comprising gravure and flexographic printing, is based on solvent-containing inks with low viscosity. Evaporation of the solvent leaves a film of pigment and polymeric binder; a porous surface is not required to absorb the ink. In the second group of printing methods, consisting of the letterpress and offset processes, paste inks made with linseed oil or similar drying oils are used. These inks do not dry by evaporation of a solvent, but by oxidative crosslinking of the unsaturated drying oil, a very slow process. Unless the printing ink can penetrate into the substrate, it will take a long time until the printed object can be handled. It is therefore necessary for the letterpress and offset printing methods to have a substrate with a porous surface, and polymer films must be modified accordingly.

One type of surface treatment to improve the printability is the application of a pigment coating. In the paper industry, the improvement of the surface of cellulose paper with a pigment coating has been known for some time. Typical binders for these coatings are casein, polyacrylates, or copolymers of butadiene and styrene. China clay, barium sulfate, chalk, or titanium dioxide are used as pigments. Coated papers are particularly well suited for art prints. In spite of their closed, smooth surface they are sufficiently absorptive for letterpress and offset printing because of their high content of mineral filler. Coated polymer films have similar properties; they can also be used for all printing processes, and the print quality is equal to that of coated papers.

Coatings for polymer films usually differ somewhat from those used for paper. The binders are the same, but less binder is used since it cannot penetrate into the film and is therefore fully available for the formation of the pigment coating. In some cases, particularly with polyolefins, the surface of the film must be oxidized by corona treatment or flaming to improve the adhesion of the coating. Conventional paper-coating machines can be used to apply the coating, but it may be necessary to modify the drying section because of the relatively low distortion temperatures of the polymer films.

There are also other methods through which the printability of film surfaces may be improved. In 1937, a patent was issued which describes a method to improve the printability of polystyrene through the action of solvents[4]. In the meantime, other patents have appeared[5-7] which are also concerned with the effect of solvents on polymer films. It is possible to produce porous surface layers which equal cellulose paper in their ability to absorb ink. Through variation of solvent and reaction time, one can adjust the depth of the porous layers as well as the pore size. Examples of possible applications of this method are shown in Fig. 8.

For gravure and flexographic printing it is not necessary to have a porous surface, since the printing inks dry through evaporation of the solvent. However, conventional printing inks, which were developed for paper, frequently adhere poorly to polymer films. This problem can sometimes be solved by the use of special printing inks. Another possibility is to increase the polarity of the polymer surface by oxidation, either with a corona discharge or by flame treatment. These methods have been used successfully for a number of years, especially with polyolefins. In practice, in-line units are used where the film is treated immediately after extrusion. Ink adhesion can also be improved by mechanical grinding which roughens the surface and enlarges the surface area.

Thus, in principle, all polymer films can be printed on, either with special printing inks or after surface treatment. If the proper method is selected, the polymer films equal or surpass cellulose paper in ease of printing and print quality.

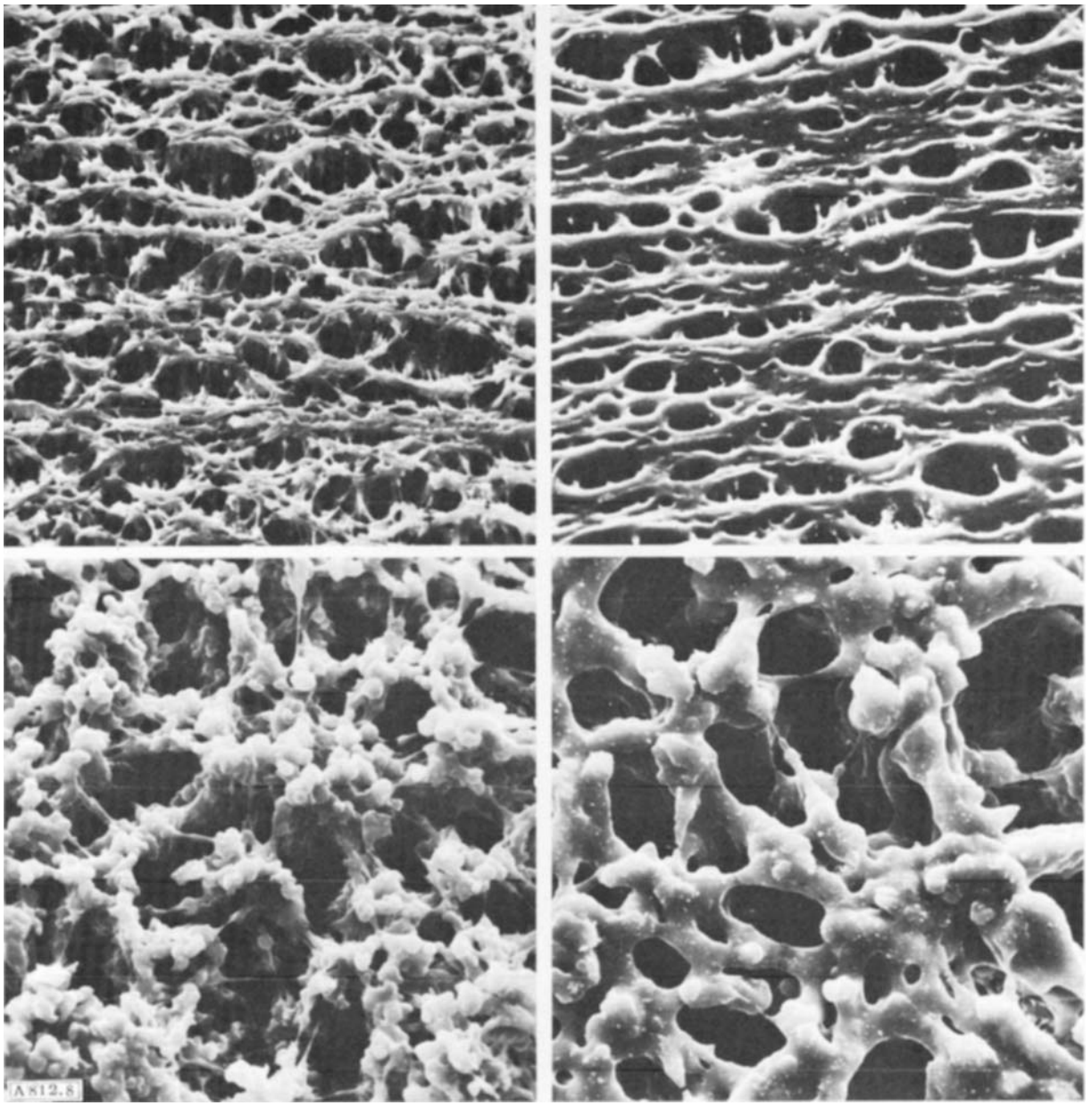


Fig. 8. High impact polystyrene film treated solvents (Stereoscan pictures). Enlargement 500:1. Solvents: acetone (upper right, lower right); acetone/water (lower left); acetone/methanol (upper left); duration of treatment 1–5 s.

3.5. Commercial Products

Extruded polymer films have been commercially available for some time, unoriented as well as biaxially oriented. Films specifically developed for use as synthetic paper, however, have only been marketed in recent years. The first product of this type was produced by Union Carbide Corporation under the trade name Ucar®. It is a film made from high density polyethylene with a high pigment content; similar products have more recently appeared under the names of Acroart® and Polyart®. Most of the recent developments of paper-like films come from Japan[8–10].

Table 3. Commercially available synthetic paper made by extrusion.

Name	Producer	Raw material	Printability through	Applications
Q'Kote®	Japan Synth. Paper Co.	polystyrene	pigment coating	art printing
Q'Per®	Japan Synth. Paper Co.	polystyrene	solvent treatment	writing and printing
Printel S®	Sekisui Chemical Co.	polystyrene	pigment coating	art printing
Ucar®	Union Carbide Corp.	HD-polyethylene	pigmentation	art printing
Acroart®	Mead Paper Corp.	HD-polyethylene	pigmentation	art printing
Polyart®	Bakelite-Xylonite Ltd.	HD-polyethylene	pigmentation	art printing
Finoplas®	C. K. Addison Ltd.	HD-polyethylene	pigmentation	tissue paper
HM-Folie®	Farbwerke Hoechst	HD-polyethylene	pigmentation	tissue paper
Tissuethene®	MGS Plastics Ltd.	HD-polyethylene	pigmentation	tissue paper

They are predominantly pigment coated biaxially oriented films made from high impact polystyrene (Q'Kote® and Printel S®) or solvent-treated films made from polystyrene (Q'Per®). Table 3 summarizes the most important commercial products; completeness is not claimed.

The cost of paper made from polymer film is still considerably (50–150%) higher than the corresponding cellulose paper[8], mainly because of the higher cost of the raw materials. It can be expected, however, that the more rapidly rising cellulose prices will change this situation in favor of the paper made from polymer film.

4. Applications

4.1. Packaging Materials

The rapid developments in the packaging field in the past few years have led to an increasing competition between packaging made from paper and from plastics. Important factors for using plastics are their complete indifference toward moisture, the availability of different degrees of transparency, and their resistance toward bacteria. A more recent application in the packaging field, in which the paper-like quality of the polymer films is more apparent, is synthetic tissue paper[11]. These extremely thin films, used mostly for wrapping flowers, shoes, and textiles, are made from high density polyethylene *via* the blown film technique. In feel and appearance they are quite similar to tissue paper made from cellulose. Since there is usually no need to print on them, a special treatment of the surface is not necessary.

Foamed film made from polystyrene has found acceptance for the packaging of eggs, meat, and fruit; it is also used for the production of drinking cups. Apart from its excellent thermal insulation and shock absorbing qualities, this film has the advantage that it can be given the desired shape by deep drawing.

4.2. Printing Substrates

By far the most interesting application of synthetic paper is as substrate for printing. It is simply a matter of price that has prevented its reaching greater economic significance in this area. Since all synthetic printing substrates, fiber webs as well as extruded films, are still considerably more expensive than cellulose paper, they are used only in applications where their special properties are needed and where they can command a higher price.

Synthetic fiber webs, the most expensive of the synthetic papers, are distinguished by their high tear strength, high folding endurance, resistance to yellowing, and high wet strength. Brochures of the manufacturers mention maps, identification papers, tags, and similar items as possible applications.

Extruded films for use as printing substrates have been available only for a short time. Because of several desirable properties, they have already found a number of applications. Their excellent dimensional stability makes them suitable for computer cards, recording paper for instruments, and other uses where constant dimensions are important. They can also be made with good transparency, which suggests their use as tracing paper.

5. Prospects

The technical problems in fabricating synthetic paper and making it printable have largely been solved. Further developments will deal mainly with the optimization of existing processes and with the reduction of costs by using larger production units. A problem which still remains to be solved is the disposal of synthetic paper waste. Waste cellulose paper is used to a large extent for the production of cheaper grades of paper and cardboard. Reusing synthetic paper will be difficult since it not only must be separated from cellulose paper, but also must be sorted according to the type of polymer used, such as polystyrene, polyethylene, *etc.* The only practical solutions may be combustion or deposition with solid refuse.

Of great interest, not only to the paper manufacturers, but also to the producers of the thermoplastic polymers is the potential share of the synthetic paper in the paper market. The only prognosis available comes from Japan. A much cited publication of the Resources Investigation Council, Science and Technology Agency[12] gives the figures shown in Table 4.

Table 4. Estimated share of synthetic paper in the total consumption of paper in Japan [12].

Application	1973		1978	
	Share (%)	Amount (10^3 t)	Share (%)	Amount (10^3 t)
Packaging	13	91	33	290
Cardboard	3	115	25	1480
Printing paper	3	42	23	420
Tracing paper	9	12	46	100
Others	6	36	30	230
Total		296		2520

The basis for this Japanese prognosis is the increasing shortage of wood and the ensuing increase in the price of cellulose, as compared to constant or even slightly falling prices for plastics. It is also assumed that the cost of manufacturing synthetic paper can be decreased by improvements in the processes and by large scale production. The combination of these factors, according to the above

[1] Das Papier *23*, 441 (1969).
[2] Mod. Plastics *48*, 93 (1968).
[3] *J. Jack*, Brit. Plastics *1961*, 312.
[4] Brit. Pat. 440926 (1936), Siemens & Halske.
[5] DOS 1800108 (1968), Nippon Kakoh Seishi K. K.
[6] DOS 1806168 (1968), N. K. Synthetic Paper Co., Ltd.
[7] DOS 1903940 (1970), Sumitomo Chemical Co., Ltd.
[8] *C. Saikaishi*, Jap. Chem. Quart. *V-1*, 49 (1969).
[9] *S. Imoto* and *Y. Nakamura*, Jap. Plastics *1*, 26 (1969).
[10] Chem. Eng. News *48*, No. 2, p. 15 (1970).
[11] *V. Wright*, Mod. Plastics *50*, 59 (1970).
[12] Resources Investigation Council, Science and Technology Agency: Synthetic Paper in Japan. The Society of Polymer Science, 1969.

forecast, will bring the price of synthetic paper close to that of cellulose paper.

The realization of the above figures for the production of synthetic paper would require not only a tremendous increase in the capacities for the production of thermoplastics, but also for the starting materials benzene, ethylene, and propylene. It would also require an acceptable solution to the disposal problem.

The question arises as to how far the Japanese prognosis can be applied to other countries. Regrettably, similar studies for Europe or America do not exist. However, it seems likely that, at least initially, synthetic paper will play a much smaller part in these areas. Cellulose prices are generally lower than in Japan, and there has been no development effort of comparable intensity. For most applications, synthetic paper will be too expensive, even if the still uncertain question of its cost is interpreted optimistically. Only the future can tell whether synthetic paper will find a substantial share of the market in some special applications.

We are indebted to Dr. H. Hendus for the stereoscan pictures.

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Synthesis of Heterocyclic Ring Systems for Heat-Resistant Plastics from Polyisocyanates

By Rudolf Merten[*]

Investigations on space flight and rockets carried out in particular in the United States have aroused great interest in plastics with enhanced thermal stability. It has become possible to pass far beyond the expected limits of thermal stability with organic plastics, and to synthesize plastics and polymers that can be used at temperatures between about 200 and about 500 °C, a range that formerly appeared to be the exclusive province of inorganic materials.

1. Introduction

The thermal stability of organic compounds is largely determined by the basic structural units. Polymers with recurring heteroaromatic units are extremely stable to heat, especially when these rings are fused to other aromatic systems. However, this structural feature is not essential for high thermal stability, as will be shown below.

The expression "heat resistance of plastics" can be construed in various ways. It may be taken to mean that the melting or softening point is high (above about 250 °C), that the decomposition point is high, or that a high stability up to high temperatures is found in differential thermal analysis or in thermogravimetric investigations. On the other hand, the mechanical and physical properties of plastics both after brief exposure to high temperatures and after prolonged aging are vital to their practical use (see Section 6). Reviews on these general questions have been published[1, 2].

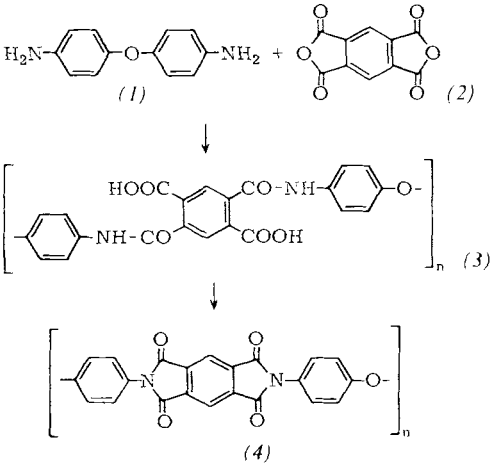
The present progress report will deal with syntheses of heat-resistant plastics from polyisocyanates, with particular reference to practical applications in the field of electrical insulation.

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2. Polyimides

The first important contribution in the field of polymers with enhanced heat resistance was the polypyromellitimides, which were developed primarily by Du Pont. Pyromellitic dianhydride *(2)* reacts with 4,4'-diaminodiphenyl ether *(1) via* polyamidecarboxylic acids *(3)* to form polypyromellitimides *(4)*, which have found extensive use in various forms (Capton H as a film, Pyre ML as a paint component, and Vespel as a plastic).

The difficulties associated with the synthesis of such plastics in practice are evident even in this system. Because

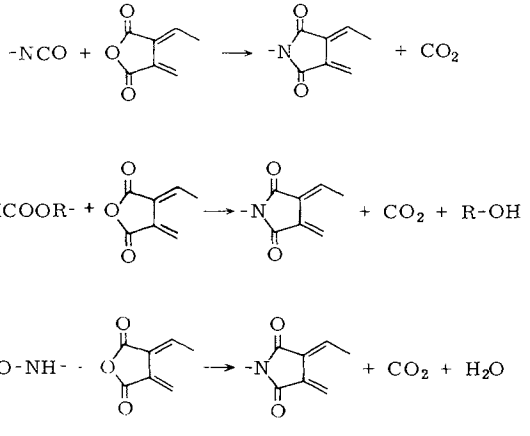


(1) *(2)* *(3)* *(4)*

of their high softening points (above 250 °C), these plastics can be processed by the methods used for thermoplastics only under very special conditions. Processing as solutions is more generally applicable, but this usually necessitates the use of precursors. The final polymers are practically insoluble in common industrial solvents; solubility in *e.g.* concentrated sulfuric acid or chlorosulfuric acid is of little practical interest.

Since the service properties, particularly the elastic behavior, are satisfactory only for products with high molecular weights, these precursors must be capable of being condensed to a sufficiently high degree; this is a problem that can often be solved only by expensive and complicated purification operations. Thus polypyromellitimide *(4)* is always converted into the final polymer only after molding in the amidecarboxylic acid state *(3)*. This presents complications because of the poor hydrolysis resistance of the intermediate *(3)* [and water is eliminated in the cyclization to form *(4)*] and because of the necessary purification of the starting material. Another disadvantage, the seriousness of which varies according to the field of application, is the rather high wastage rate during further processing, *e.g.* for film material, since the material is practically insoluble after cyclization.

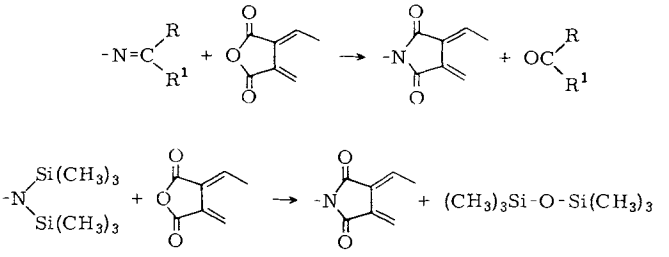
The use of "masked" amines offers considerable advantages in the synthesis of polyamide systems. Such "masked" amines are all less basic than the parent substance, and can be obtained more readily in the pure state. Moreover, they react much more slowly with the anhydride groupings, thus making stepwise reaction possible. Another advantage in some cases is the elimination of inert, volatile by-products, which cannot interfere with the reaction (see Section 6.2).



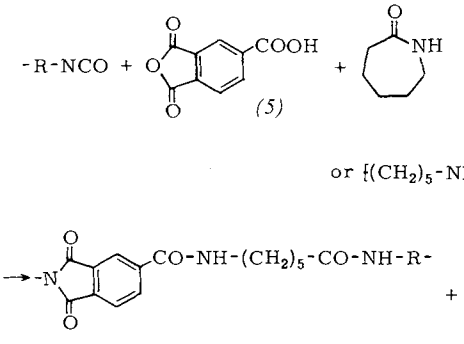
R = Aryl, Alkyl

The most interesting variants of the "masked" amines are the isocyanates[3]. They react with an anhydride grouping with elimination of carbon dioxide as an inert component to form the imide; the reaction is readily controlled between 120 and 200 °C. Instead of the free isocyanates, compounds that react as isocyanates only at high temperatures and that may allow further variation of the course of the reaction in combinations can be used with equal or in some cases better success. Examples of such compounds are *O*-aryl and *O*-alkyl esters of carbamic acids or the ureas from which the isocyanates are derived.

Instead of as isocyanates, the amines can also be used in the form of aldimines or ketimines[4] or as *N,N'*-bis(trimethylsilyl)derivatives[5]. The condensation with the anhydrides proceeds with elimination of oxo compounds or of hexamethyldisiloxane.



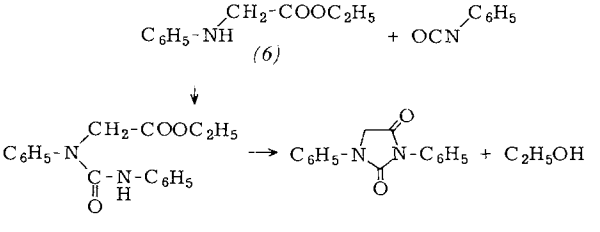
The above methods can be used to make a desired polymer containing imide groups while providing for further variation by incorporation of additional functional groups. The pure polyimides (obtained from pyromellitic acid), the polyamide-imides (from trimellitic anhydride), and such polymers modified by introduction of ester groups appear of especial interest. A variant of particular industrial significance results on use of caprolactam and its polymers in condensations between anhydrides and isocyanates or "masked" isocyanates[6]. The overall reaction is shown for trimellitic anhydride *(5)*.



3. Polyhydantoins

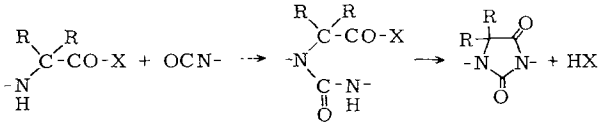
In the polyimide plastics and the other known heat-resistant systems, the heterocyclic units always possess aromatic character, and are also fused to aromatic systems. However, nonaromatic systems can also have high thermal stabilities, as we have been able to show in particular for polyhydantoins.

Several methods are now known for the synthesis of polyhydantoins[7,8]. Apart from the polymerization of *N*-vinylhydantoins[9], the addition of HCN to diisocyanates[10], and condensation of bishydantoins with formaldehyde[11],



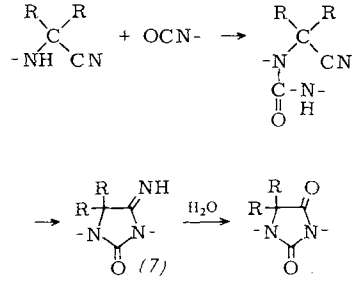
the reaction of *N*-phenylglycine esters *(6)* with phenyl isocyanate, which was described in principle by *Wheeler* and *Hoffman*[12] in 1911, now plays an important part[7, 8].

This reaction is of a general nature, and can be used for the synthesis of polymers from polyfunctional glycine esters and polyfunctional isocyanates (or their derivatives).



X = OCH_3, OC_2H_5, $N(CH_3)_2$, NH_2, OH

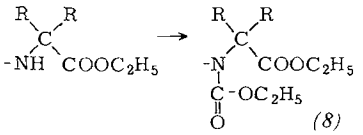
A variant of this method is the reaction of glycinenitriles with isocyanates[13]. The ureas obtained cyclize to form "iminohydantoins" *(7)*, which afford the hydantoins on hydrolysis. This path is particularly suitable for the preparation of low molecular weight hydantoins, which then react by means of functional groups to form polymers.



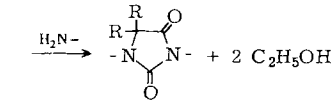
(7)

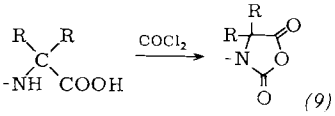
Further possibilities for the synthesis of the hydantoin ring are offered by the use of glycine-*N*-carboxylic acid derivatives, *e.g.* the esters *(8)*[14] and the anhydrides *(9)*, which also react with amines and isocyanates to give hydantoins. However, the last two methods have proved to be less suitable for the synthesis of high molecular weight compounds, since the polyfunctional starting materials are too difficult to obtain in the pure state.

The above methods have been used for the preparation of many monomers and oligomers containing other reactive groupings, which allow the formation of polymers, besides

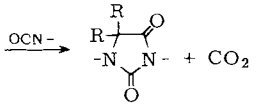


(8)

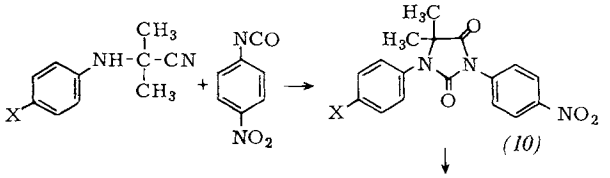




(9)

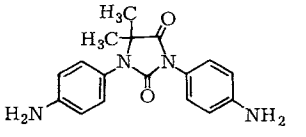


the hydantoin groups. Several possibilities of this type are indicated in the following formulas and in Scheme 1 (see also[13, 15]).



(10)

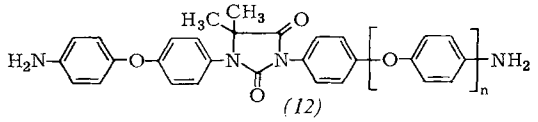
(10a), X = H; m.p. 214-215 °C
(10b), X = NO_2; m.p. 228-230 °C
(11) m.p. 279-280 °C



(11)

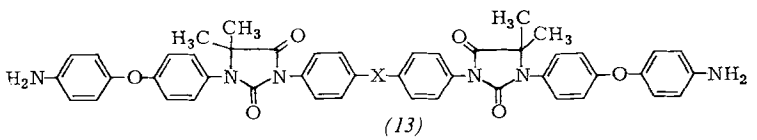
Other functional groups can be introduced *via* the isocyanates, *e.g.* by the use of isocyanates that also contain ester groups, unsaturated groupings, or even additional isocyanate groups.

Another variant of the preparation of oligohydantoins containing functional groups begins with esters of aspartic acid. Primary amines add smoothly to maleic and fumaric esters to form aspartic esters *(15)*; subsequent reaction with (poly)isocyanates again yields hydantoins containing ester groups. Polyfunctional derivatives are obtainable, *e.g. via* polyamines or polyisocyanates[16].



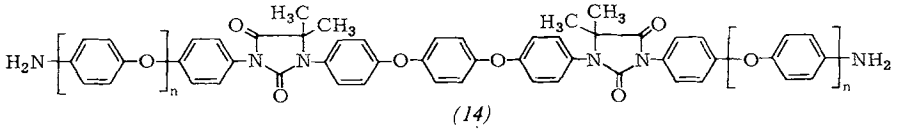
(12)

(12a), n = 0; m.p. 258-259 °C
(12b), n = 1; m.p. 188-195 °C



(13)

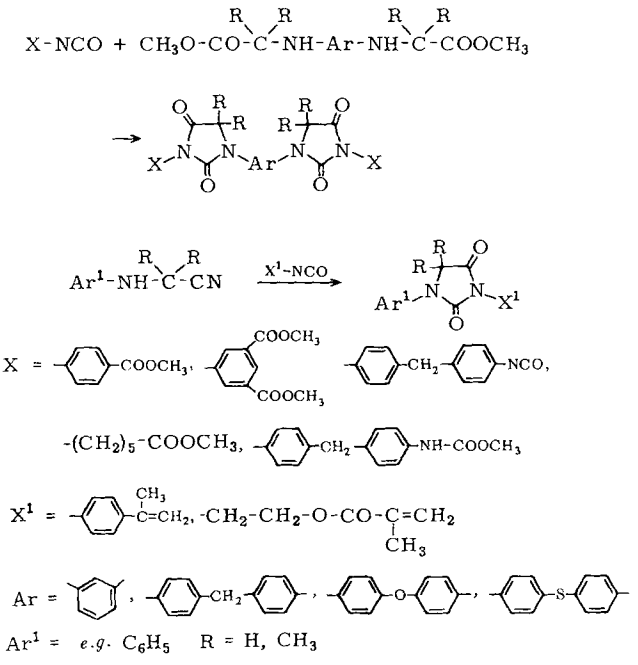
(13a), X = -O-⟨⟩-O-; m.p. 150-154 °C
(13b), X = -O-⟨⟩-SO_2-⟨⟩-O-; m.p. 173-181 °C



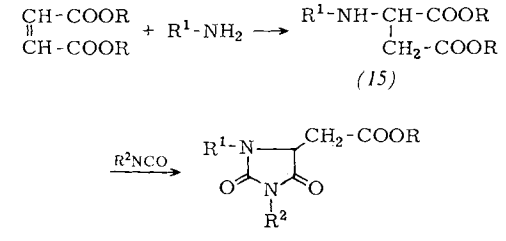
(14)

(14a), n = 0; m.p. 300-303 °C
(14b), n = 1; m.p. 258-262 °C

Scheme 1. Examples of heat-resistant oligohydantoins.



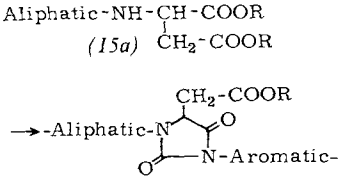
The synthesis paths described lead to more or less high molecular weight compounds containing hydantoin rings, which also contain functional groups that allow conversion into more highly polymeric systems. Polyamides and polyimides can be prepared in this way from these "oligohydantoins" containing free amino groups (*e.g.* with isophthaloyl chloride or pyromellitic dianhydride). Phosgenation of the aminooligohydantoins leads to polyfunctional isocyanates, which can be made to react further by the methods of polyurethane chemistry. Oligohydantoins containing carboxylic acid groups can be modified by esterification or aminolysis. Unsaturated compounds of this series can be homopolymerized or copolymerized.



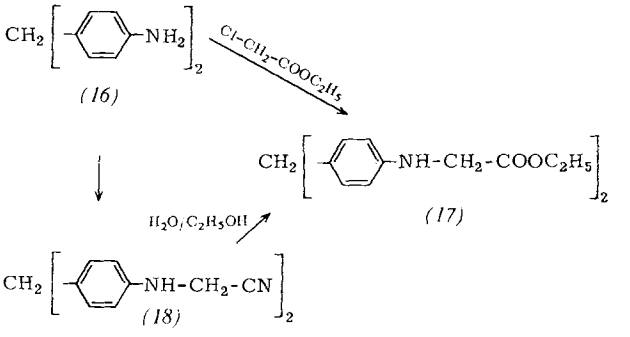
Polyhydantoins can also be obtained by a polymer-forming reaction of the addition-condensation type involving the reaction of compounds containing at least two glycine ester groups with polyisocyanates.

Two particularly useful methods for this purpose are the reaction of maleic (fumaric) esters with diamines and diisocyanates and the reaction of aromatic bisglycine esters with polyisocyanates.

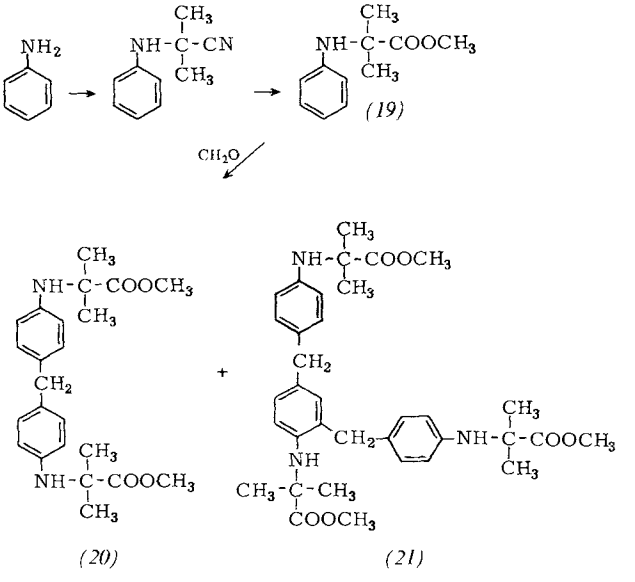
The first method leads in the most favorable case to mixed aliphatic-aromatic polyhydantoins, whose heat resistance is reduced by the aliphatic components. (It is difficult to obtain sufficiently high yields in industry when aromatic diamines are used in the addition reaction, since these compounds do not add readily.) However, the method is fascinating in its simplicity. The amine component is added dropwise to the maleic ester in cresol; after the addition to form *(15a)*, the aspartic ester derivative, the diisocyanate is added and the compounds are condensed at the boiling point of cresol. The resulting solutions of polyhydantoin in cresol can be used directly for the preparation of electrically insulating varnishes with softening points above 330 °C.



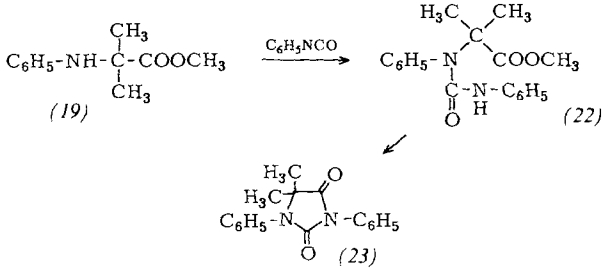
The addition of diisocyanate to aromatic bisglycine esters leads to polyhydantoins with exclusively aromatic linkage. The starting compounds can be prepared by well-known methods; aromatic diamines *(16)* react with chloroacetic ester in the presence of bases such as $CaCO_3$ to form bisglycine esters *(17)*. The same compounds can be obtained by Strecker synthesis *via* the nitrile *(18)*, with subsequent hydrolysis.



Polyglycine esters derived from bis(aminophenyl)methane, such as *(20)*, can also be obtained from aniline *via* anilinoisobutyric ester *(19)* by condensation with formaldehyde. The simultaneously formed trisglycine esters *(21)* may be useful in the preparation of branched or crosslinked polyhydantoins.



Difficulties arise in the reaction of glycine esters with isocyanate, since the amino group in the glycine ester reacts only slowly with the isocyanate. Moreover, it is necessary to avoid the cyclization of the urea intermediate *(22)* before the addition is complete, since there is otherwise a possibility of a competitive reaction with the liberated alcohol to form urethane. The desired molecular weights of *e.g.* more than 15000 for lacquer components and more than 25000 for films require 96 and 98% definite reaction, respectively, between the two components. These problems have been solved by the choice of catalyst and reaction medium.



(19) *(22)* *(23)*

The system phenyl isocyanate/anilinoisobutyric ester *(19)* was used for kinetic investigations. The results show that the usual views on the catalysis of isocyanate reactions are inapplicable (Table 1 and Fig. 1).

Table 1. Conversion of phenyl isocyanate in the reaction with methyl anilinoisobutyrate *(19)* (5 hours, 20°C, in dichloromethane) on addition of 1 mole-% of catalyst (in 1 N solution).

Catalyst	Conversion (%)	Catalyst	Conversion (%)
none	17	BF_3-ether	43
Iron(III) chloride (sublimed)	15	Phenol	62
		Formic acid	49
Boric acid	16	Acetic acid	88
Trifluoroacetic acid	21	Propionic acid	87
p-Toluenesulfonic acid	39	Benzoic acid	85

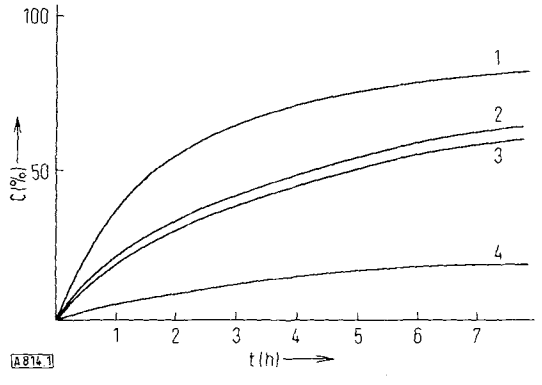
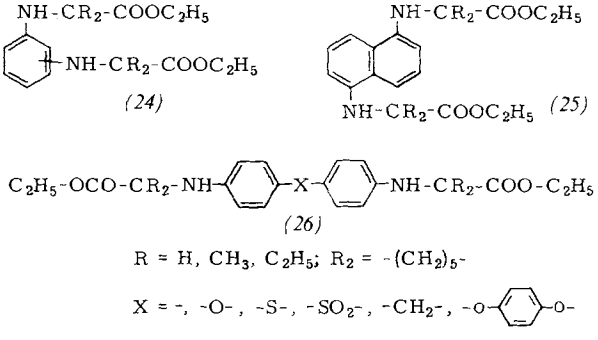


Fig. 1. Conversion of phenyl isocyanate in the reaction with methyl anilinoisobutyrate *(19)* (20°C, in dichloromethane) on addition of 1 mole-% of catalyst (in 1 N solution).
Catalysts: 1: acetic acid; 2: 1,4-diazabicyclo[2.2.2]octane; 3: phenol; 4: none.

A reasonable catalytic effect is observed only when compounds of "medium acidity" (carboxylic acids, phenols) are used, and this effect is sufficient only when these compounds are used as solvents. Because of the tendency toward ring closure when basic substances are used, as well as the side reactions of NCO groups in the presence of carboxylic acids or amines, phenols are practically the only "active" solvents left. The condensation reactions to form the aromatic polyhydantoins in the production of polymers are thus best carried out in phenol or cresol, particularly since the polymers are readily soluble in these solvents (they are not very soluble in other solvents, apart from CH_2Cl_2 and similar compounds).

With the aid of these precautions, numerous polyhydantoins have been prepared from polyglycine esters such as *(24)*, *(25)*, and *(26)* with polyisocyanates[17], and heterocycles may also be fused on[18].

By means of the methods described earlier for the introduction of functional groups, it is possible to prepare polymers having definite molecular weights and containing functional end groups, *e.g.* with urethane groups, ester groups, or polymerizable olefinic groups [by the use, either alone or otherwise, of more than or less than the equivalent molar



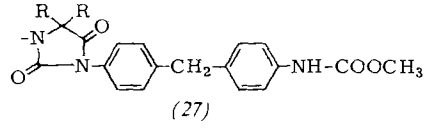
(24) *(25)*

(26)

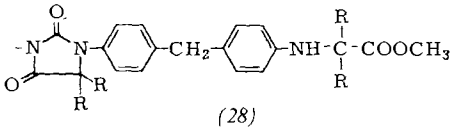
R = H, CH_3, C_2H_5; R_2 = $-(CH_2)_5-$

X = -, -O-, -S-, $-SO_2-$, $-CH_2-$, -o--o-

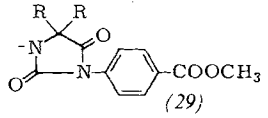
quantity of isocyanates, esters of isocyanato acids, or isocyanatoolefins; examples are *(27)–(30)*], which can then be condensed further or crosslinked by means of these functions, *e.g.* on application of the lacquer.



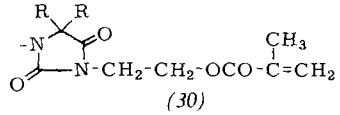
(27)



(28)



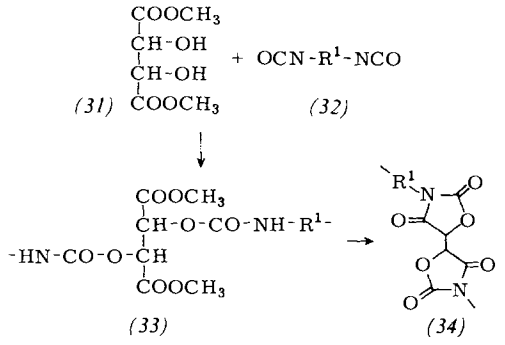
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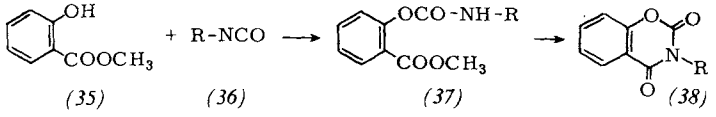
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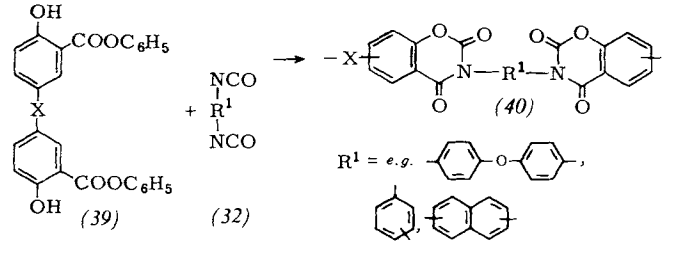
4. Polyoxazolidinediones, Polyquinazolinediones, and Polybenzoxazinediones

Instead of α-amino acids, esters of α-hydroxy acids can also be used for the preparation of heterocyclic polymers. The reaction of a tartaric acid ester *(31)* with a diisocyanate *(32)* can be used to obtain the polyoxazolidinedione *(34)* *via* the urethane intermediate *(33)*[19].



A similar reaction sequence can be applied to homologous systems in the aromatic series and used for the preparation of polyquinazolinediones[20] and polybenzoxazinediones such as *(40)*[21]. In this case, the heterocycles are condensed with an aromatic system, and the expected high heat resistances are obtained. Out of several methods that are available for the preparation of this class of substances, the reaction of an *o*-hydroxy acid ester *(35)* with an isocyanate *(36)* is particularly interesting; it leads to the benzoxazinedione *(38) via* the *O*-arylurethane *(37)*, which cannot always be isolated. The application of this reaction to polyfunctional *o*-hydroxy acid esters, such as the phenyl esters of methylenedisalicylic acid, 4,4'-dihydroxybiphenyl-3,3'-dicarboxylic acid, or 2,5-dihydroxyterephthalic acid [generally obtainable by Kolbe syntheses from phenols], *e.g.* *(39)*, and polyisocyanates such as *(32)* yields the polybenzoxazinediones *(40)*. The reaction is carried out in polar solvents such as dimethyl sulfoxide, generally with amine catalysts. On elimination of phenol, the polymer *(40)* can be isolated directly, *e.g.* by precipitation.

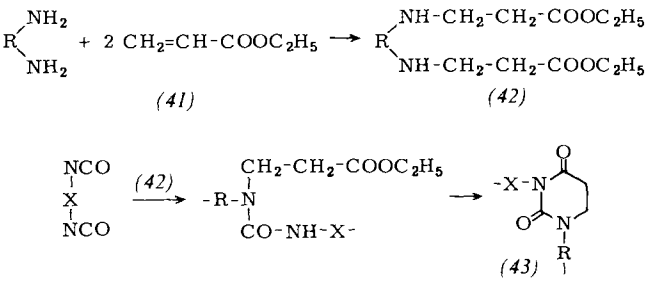




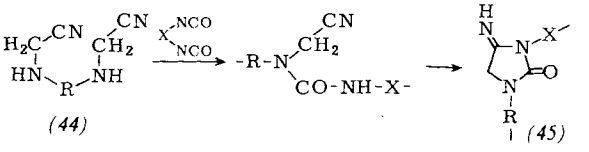
The final polymer can be *e.g.* cast from solutions in polar solvents such as dimethylformamide and dimethyl sulfoxide to form films, the solubility of which depends on the starting components.

5. Polydihydrouracils and Polyiminoimidazolidinones

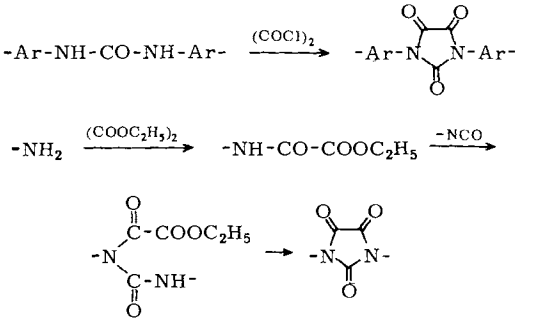
The addition of acrylic esters *(41)* to polyamines followed by addition of polyisocyanate yields polydihydrouracils *(43)*. The results of such condensations were described in detail by *Dyer* and *Hartzler*[22]. These authors[22] have also



reviewed the synthesis of polyiminoimidazolidinones by reaction of polyfunctional α-amino nitriles *(44)* with polyisocyanates.

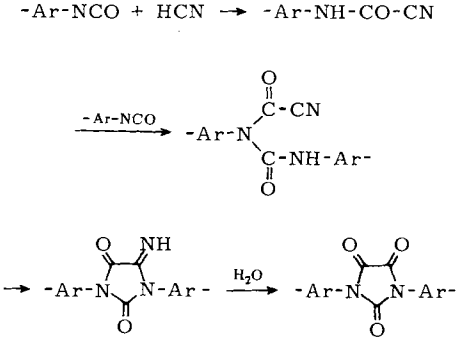


Also of interest are polymers containing parabanic acid linkages (polytriketoimidazolidines). They can be prepared by a variety of methods, *e.g.* by reaction of polyureas with oxalyl chloride[27] or by a route resembling the synthesis



of polyhydantoins from amines, diethyl oxalate, and isocyanate *via* an oxamic ester intermediate[28].

Furthermore, polyparabanic acids may also be prepared from polyisocyanates and hydrocyanic acid[29] in aprotic solvents and in the presence of cyanide ion as catalyst. The reaction proceeds *via* "iminoparabanic acid" intermediates.



6. Applications

6.1. Electrical Insulators

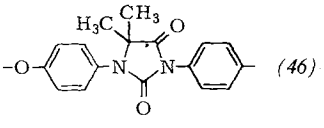
The possible uses of the heterocyclic systems mentioned will merely be outlined. Table 2 gives values[21, 23] for properties that are important in electrical insulators.

Table 2. Properties of heat-resistant plastics.

Product	Softening point (°C)	Heat shock [a] (°C)
Polypyromellitamide-imide	380–400	300
Polyhydantoin	380–400	280–300
Ester-imide (depending upon imide content)	285–360	180–260

[a] Heat shock (Brit. Standard 3160 5e, USA Standard C 9100 1968): A specimen of the coated wire is wound around a mandrel having the same diameter as the wire and heated for $^1/_2$ hour in order to determine the temperature at which no cracking occurs.

Polyhydantoins can also be used as insulating films, the advantages here being in the use of halogenated hydrocarbon solvents (methylene chloride). The hydantoin ring is resistant to temperatures up to 400 °C; to meet the requirements for insulating films, the hydantoin rings must be joined by heat-resistant and oxidation-resistant links. A group that has proved useful for this purpose is the 4,4'-disubstituted diphenyl ether residue, which leads to repeating units such as *(46)*. The same is true of polybenzoxaziniediones, which are sufficiently soluble to be processed in polar solvents such as dimethylformamide.



(46)

Long-term heat resistance tests lead to values between 165 and 180 °C, the polybenzoxaziniediones falling near the upper limits; polypyromellitimide (Capton H) withstands 210–250 °C. The dielectric and mechanical properties of both classes are practically constant up to temperatures far above 200 °C.

Experimental details in connection with the possibilities described may be found in the literature cited.

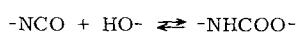
6.2. Heat-Resistant Foams

As was mentioned earlier, foamed plastics with high softening or melting points are gaining in importance, particularly since these products are all incombustible or nearly so.

The reaction of anhydride groupings and carboxylic acid groups with isocyanate groups (see Section 2) proceeds with liberation of carbon dioxide, which can in some cases be used as the blowing agent for the polymer being formed[24]. For example, by heating a mixture of trimellitic anhydride and diphenylmethane diisocyanate to about 200 °C, it is possible to start a slightly exothermic reaction, which leads to a foam containing amide and imide groupings. These foamed plastics have high thermal stabilities and are practically incombustible. The difficulty in this process for the production of imide foams lies at present in the high initiation temperature and the heat evolved, which makes the reaction difficult to control on a large scale.

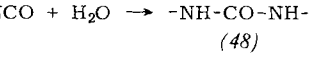
Polyisocyanurate foams, *i. e.* foams consisting essentially of isocyanurate rings linked by aromatic structures, are more favorable in practice.

A rigid polyurethane foam is generally prepared by reaction of an isocyanate with a polyalcohol to form a urethane grouping *(47)*. The foam structure is produced by addition of low-boiling foaming agents such as chlorofluoromethane. In exceptional cases even water may be used; the product then contains urea structures *(48)*. Since the reaction leading to the urethane grouping *(47)* is reversible, the



(47)

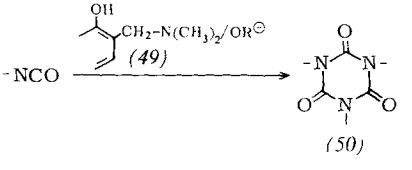
heat stability of the resulting foams is limited because of decomposition into the polyol and the isocyanate (or its reaction products). Moreover, the resulting low molecular



(48)

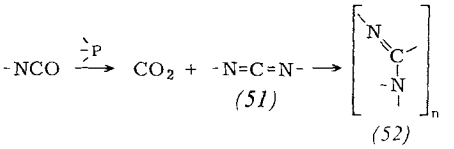
weight fragments and their decomposition products make the polymer combustible. The polyol component plays a particularly important part in this respect.

These difficulties do not arise with the isocyanurate foams, which are obtained by polymerization of the isocyanate to form trimeric structures *(50)*. Despite the pronounced branching, the polymers are relatively elastic, owing to the absence of hydrogen bonds. In addition to this isocyanurate formation, there is some conversion of the isocyanate groups into carbodiimides *(51)*, which are converted more



(49)

(50)



(51)

(52)

or less rapidly into cyclic and linear polymerization products *(52)*. This last reaction contributes to the foaming process, and cannot be reversed by heat. Thus no decomposition into monomeric or low molecular weight fragments is possible when these foamed plastics containing isocyanurate and carbodiimide groups are heated. Though the isocyanurate formation is reversible at relatively high temperatures (250–300 °C), the resulting isocyanates evidently lose carbon dioxide under these conditions to form the carbodiimides and their reaction products, so that the polymer structure is retained.

The production of polyisocyanurate foams of this type requires the use of special catalysts[25]. These should initiate the polymerization even at room temperature without an incubation period, and the temperature coefficient of the reaction rate should be as low as possible. The foaming is also carried out in this case with the foaming agent (chlorofluoromethanes), which should evaporate slowly and uniformly. Several groups of catalysts are avail-

able, including alkali metal phenoxides and alkoxides or compounds such as *(49)* containing an *o*-dimethylaminomethylphenol grouping. The formation of carbodiimide groups can be catalyzed in the conventional manner[26] by phosphorus compounds, so that it is possible, by choice of the catalysts, to cause both reactions [with formation of *(50)* or *(52)*] to occur together.

Small quantities (5–20%) of high molecular weight polyols must sometimes be used as "internal plasticizers" to achieve adequate elasticity. However, these appreciably lower the softening points of the polymers obtained, and also increase their combustibility. The formulations are strongly dependent on the intended use (possible uses include insulating materials and building materials). The thermal stabilities attainable with various systems are indicated in Table 3.

Table 3. Hot bending strength of heat-resistant plastics according to the German Industrial Standard DIN 53424.

Product	Hot bending strength (°C)
Polyurethane	110
Polyurethane on cane sugar basis	110–130
Polyisocyanurate foam	
containing 10% of castor oil	190–210
containing 5% of castor oil	220
containing no additives	250

The investigations described here were partly carried out in the laboratories of Farbenfabriken Bayer. Those who took part in this work include in particular Dr. H. J. Diehr, Dr. W. Dünwald, Dr. R. Fischer, Prof. Dr. K. Ley, Dr. K. H. Mielke, Dr. R. Nast, Dr. E. Reese, Dr. W. Röhm, Dr. F. Seng, and Dr. W. Zecher.

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Some Aspects of Chemical Mutagenesis in Man and in Drosophila

By Günter Obe, Karl Sperling, and Hans J. Belitz[*]

Since mutations produced by chemicals are, like spontaneous mutations, generally transmitted by recessive factors, i. e. as they are only expressed after several generations, depending on the circumstances, it is extremely difficult to trace the true cause of such mutations, which are almost always unfavorable. However, it is possible to study the mutagenic action of chemicals in test systems, e. g. in Drosophila in vivo or in human chromosomes in vitro. Alkylating agents which damage DNA indirectly have a particularly severe mutagenic action. The present progress report contains, among other things, a comprehensive list of substances that produce aberrations in human chromosomes.

1. Introduction

To the geneticist the term "mutation" means changes in the genotype. Mutations occur spontaneously in all organisms, and those in the gametes can be transmitted to the descendants. The capacity to undergo mutation is an inherent property of genetic material, including both the genes themselves and also the chromosomes on which the genes are arranged linearly in a certain order. The significance of mutations can be considered from several aspects:

The individual development of an organism is "self-controlled", and its detailed construction is defined by genetic information in the DNA. Ontogenesis can thus be regarded as translation of the genetic code into the form of a living creature. However, the relationship of the living creature to its environment is also important if the significance of the capacity of organisms to undergo mutation is to be understood. It is only the environment that makes life possible, and at the same time it sets certain limits to the development of living creatures. The genes determine the normal response of an organism to its environment, and thus its capacity for some degree of adaptation to this environment. The adaptation of organisms is the result of their historical development and is based essentially on the effect of two evolutionary factors, the mutability and selection. The members of a species which inhabit a certain environment and thus belong to a reproducing community are called a population.

The individual members of a population certainly do not have the same genetic make-up, although they all have the same number of chromosomes and the same number of genes in each body cell. This apparent contradiction can be explained in the following way: an ovum capable of reproduction contains one set of species-specific chromosomes, it is haploid; the same applies to the male gamete (the spermatozoon). After fertilization the diploid zygote is formed, which thus contains a homologous set of paternal and maternal chromosomes. The diploid organism develops from the zygote in the course of normal cell divisions (mitoses). The haploid gametes are formed again in the gonads by reduction division (meiosis).

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In man and *Drosophila* the females have two homologous X-chromosomes, while the males have one X-chromosome and the morphologically and genetically different Y-chromosome (sex chromosomes). The other chromosomes (autosomes) are the same in both sexes (Fig. 3).

Each autosome has a set of genes, which corresponds to the set of its homologous partner chromosome. However, two homologous genes do not have to be exactly the same. If the sequence of the purine and pyrimidine bases in the DNA of a gene is changed, then the function of this gene can be modified to a certain extent or it can even be made impossible. Such changes are recorded by the geneticist as gene mutations.

The different forms a gene can take are termed alleles. In diploid cells each gene locus is represented by two alleles. If both alleles are identical (homozygous), then their external characteristics become fully developed, *i. e.* their phenotype is shown completely. However, if they are different (heterozygous), then there are several possible ways their characteristics can be expressed. New gene mutations are as a rule recessive, *i. e.* their phenotypic effect is not produced in the heterozygous state. Recessive mutations in the X-chromosome of the male sex are exceptions to this rule. There is no normal allele accompanying a mutated allele in the X-chromosome, and thus the mutations can be expressed phenotypically "in a single dose". Dominant mutations also show their phenotypic effects in the heterozygous state.

Most mutations in the homozygous state decrease the viability of their bearer, very many act as lethals and lead to death, and only very few produce an improvement. This is understandable when one considers that the mutation process is random and that each change occurring by chance in a system that is generally optimally adapted to its environment is more likely to lead to a deterioration rather than an improvement. As a result of selection, the bearers of viability-depressing alleles are eliminated or they have a reduced probability of reproducing themselves. In this way the frequency of harmful alleles in natural populations is generally low.

If a new mutation has certain advantages, its bearers have a greater probability of reproducing themselves than normal members of their species. The new allele is favored by selection; its frequency increases from generation to gene-

ration, and finally the allele from which it developed is completely eliminated.

In addition to the above-mentioned gene or point mutations, there are chromosome mutations which also play an important role; three types of these must be briefly discussed here.

The term deletion is used for the loss of a chromosome segment

ABCD → ABD

As a rule the loss of such a segment (here segment C) is lethal.

The same applies to the replacement of parts of chromosomes by nonhomologous chromosomes (translocation):

ABCD + EFGH → ABGH + EFCD

In another type of chromosome mutation a section of a chromosome is inverted through 180° to its normal position (inversion):

ABCD → ACBD

Inversions are more frequently found in natural populations than the other aberrations mentioned above.

Disturbances in the course of mitosis or meiosis can cause an irregular distribution of the chromosomes in the daughter cells. Cells with a different number of chromosomes (aneuploids) are thus formed, which as a rule disturbs the gene balance. An aneuploidy occurring spontaneously in man is the trebling (trisomy) of the small chromosome no. 21 (cf. Fig. 7), associated with Down's syndrome (mongolism).

Another type of mutation, widely distributed in plants, is the multiplication of the diploid number of complete chromosome complements (polyploidy). Polyploidy does not play any great role in the animal kingdom.

The well-known works of *Muller*[1], *Auerbach*[2] and *Oehlkers*[3] have shown that both X-rays and chemicals can produce a drastic increase in the frequency of spontaneous gene and chromosome mutations. These discoveries resulted in the development of two extensive areas of research, radiation genetics and chemogenetics.

Some results will now be reported which it was possible to obtain in a genetic and a cytological test system used to investigate the mutagenic effects of chemical substances. The test systems will first be described in greater detail in the following sections.

1.1. Drosophila melanogaster

The classical tool used in mutation research is the fruit fly *Drosophila melanogaster*, on which *Muller*[1] demonstrated the mutagenic effect of X-rays in 1927. *Muller*, who was a master in developing special strains, used at that time the famous ClB strain to demonstrate sex-linked (*i.e.* situated on the X-chromosome) recessive lethals. Later he bred a

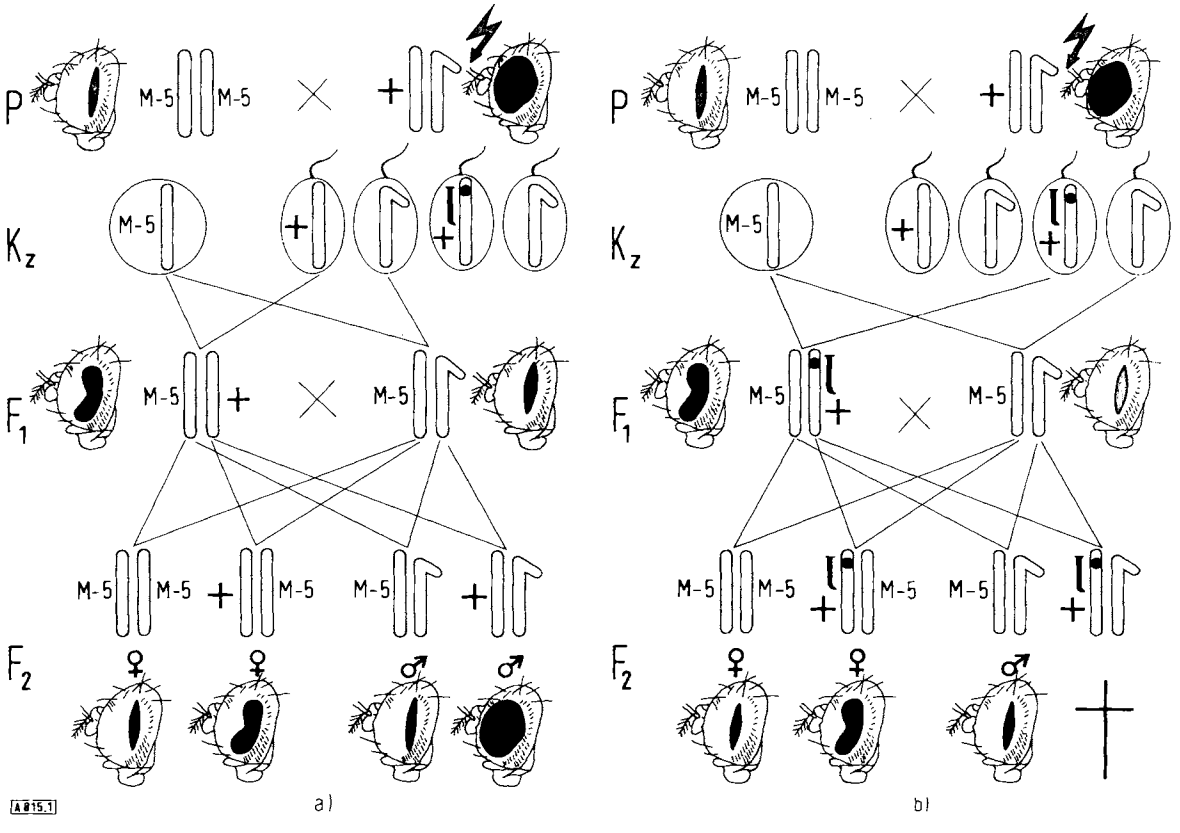


Fig. 1. The Muller-5 method for the detection of recessive sex-linked lethals in *Drosophila melanogaster*. a) Crossing with the participation of the normal X-chromosome; b) crossing with the participation of the X-chromosome with an induced lethal. The lines indicate the possible combinations at fertilization. P = parental generation; F_1, F_2 = first and second filial generations; K_z = gametes of the parental generation (the rod-like elements are X-chromosomes and the hook-like elements Y-chromosomes); M-5 = Muller-5 chromosome; + = X-chromosome of the wild type; l = recessive lethal factor; ϟ = treatment with X-rays or chemicals; † = non-appearance of normal males. (After charts of the Institute of Genetics of the Free University of Berlin.)

far better strain for the same purpose, and this has been the one generally used since 1948[4].

This special strain is known as Muller-5 (M-5) or Basc after the characteristic factors on its X-chromosome. Factor B (bar-eyes) is dominant, the two other factors (apricot-colored eyes and a bristle anomaly) being recessive. In addition, the M-5 chromosome contains two inversions.

When carrying out mutagenicity tests, normal males (with red, round eyes) are exposed to the action of X-rays or chemicals. Before the whole-body irradiation the flies are

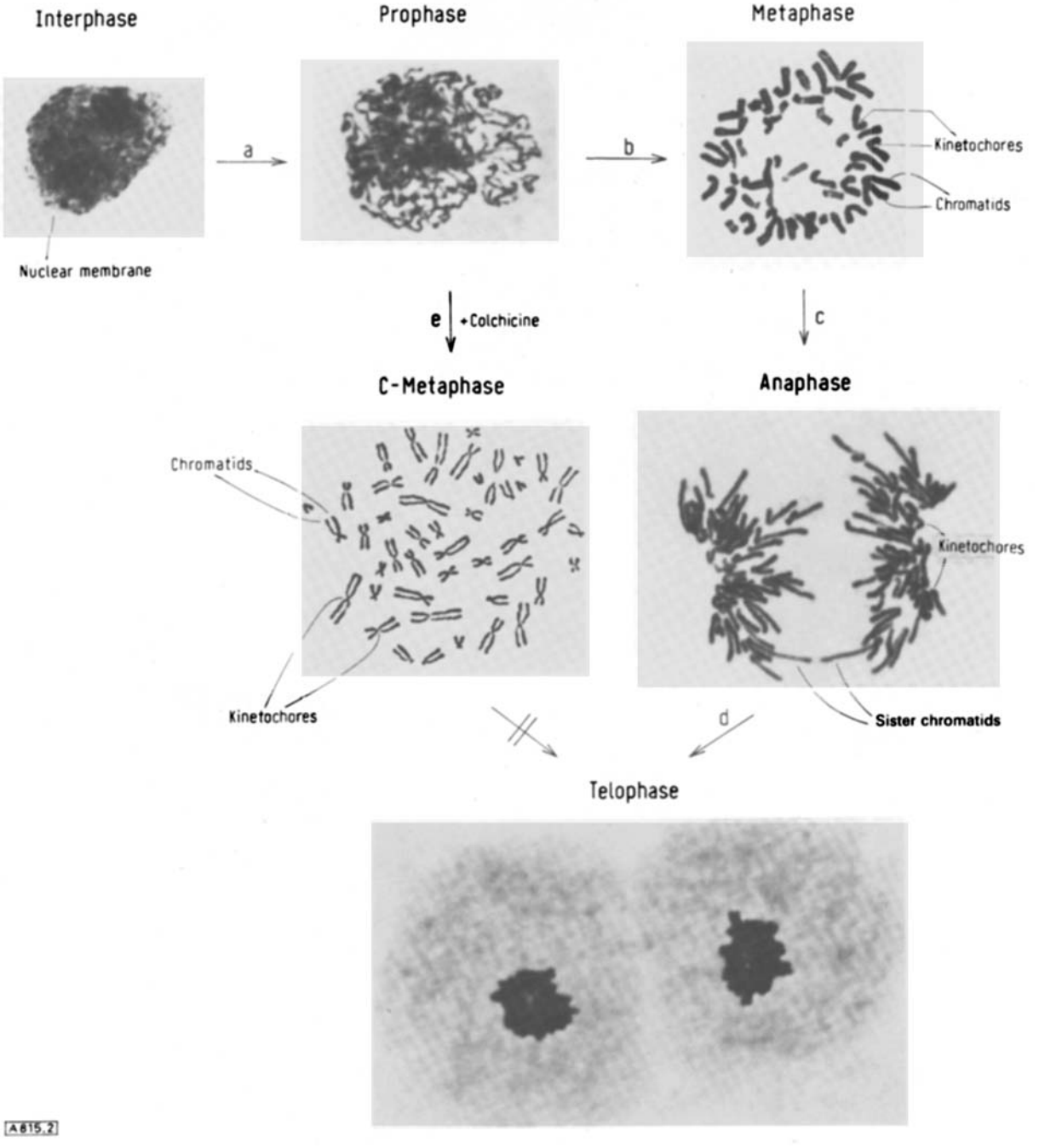


Fig. 2. Mitosis and C-mitosis (Colchicine-mitosis) of human cells *in vitro*. a→b→c→d: normal mitosis; a→e: C-mitosis.

Interphase: The chromosomes are mostly unfolded and separated from the surrounding cytoplasm by a nuclear membrane. The replication of the chromosomes occurs in a fraction of the interphase time called the synthesis phase (S-phase).

Prophase: Progressive folding up of the chromosomes makes them visible under a light microscope.

Metaphase: The nuclear membrane has disappeared. The considerably shortened chromosomes are arranged in the equatorial plane of the cell. The chromosomes are clearly seen to be composed of two chromatids connected in the region of the kinetochores. The chromosomes are arranged in a circle leaving a chromosome-free region in the middle of the equatorial plane.

Anaphase: With the kinetochores ahead, the longitudinal halves of the chromosomes move toward the opposite poles of the cell. The spindle fibers cannot be seen in these pictures. They join the kinetochore regions to the cell poles.

Telophase: The daughter chromosomes arrive at the cell poles. The daughter nuclei are formed. The plasma body divides itself in the equatorial plane.

C-Metaphase: The contraction of the chromosomes is more extensive than in a normal metaphase. Chromatids and kinetochores can be readily distinguished, especially after hypotonic treatment of the cell. The chromosomes are distributed over the whole equatorial plane.

enclosed in small gelatine capsules. The chemicals can be applied in various ways. The flies are often placed in glass filter crucibles saturated with solutions of the substances under test, and they then take the mutagen orally[5]. The dissolved substances can also be injected into the flies abdomen.

The treated males are mated individually with one or several females of the M-5 strain. The female progeny of the first generation obtain one of their X-chromosomes from their mother (M-5-X), while the other X-chromosome comes from the father and can be mutated. The males of this generation receive their single X-chromosome from their mother and look like their mother, as the Y-chromosome coming from the father contains practically no genes. The females have bar-shaped, but red eyes. Each female thus possesses *one* X-chromosome that had been treated in the initial male.

In this test system the fate of the autosomes cannot be followed further. Each female of the first generation is placed with a brother to produce the next generation, and the experiment can be evaluated 12 days later. Each culture now represents *one* X-chromosome treated in the initial males. If a lethal has been induced in one of these, then no males of normal appearance can be found in the affected culture, but only M-5 animals and heterozygous females (with bar-eyes). While the recognition of visible mutations largely depends on the experience of the investigator, the absence of a whole Mendel class cannot be overlooked (cf. Fig. 1). The overall frequency of the sex-linked recessive lethal factors can be determined very precisely with the M-5 strain.

The treated males come from laboratory strains with known spontaneous mutation frequencies. For the sex-linked lethal factors these lie between 0.07 and 1.0%, *i.e.* 7–100 new lethal mutations appear for every 10,000 gametes.

The order of magnitude of the effect of X-rays can be stated. The frequency of recessive sex-linked lethal factors in *D. melanogaster* increases to about 3% per 1000 R. However, no generalizations can be made concerning the chemical mutagens, which will be discussed in detail later.

1.2. Human Chromosomes

The chromosomes of the higher organisms undergo a characteristic change in shape during cell division (mitosis). Under a light microscope they can be examined best at the stage of maximum contraction (the metaphase). This condition is fulfilled best in the colchicine metaphase (C-metaphase)[6, 7]. Colchicine prevents the distribution of the chromosomes to the daughter cells, as the spindle fibers necessary for this purpose are not formed. The two identical split halves of the chromosomes, the chromatids (the replication of chromosomes occurs during the interphase stage when no division is taking place), remain connected to each other at the spindle fiber attachment site (kinetochore), as is shown with human chromosomes in Figure 2.

Colchicine does not inhibit the dissolution of the nuclear membrane, and the chromosomes are dispersed over the whole equatorial region of the cell. Treatment with a hypotonic salt solution (for example 0.9% sodium citrate) during the course of the preparation increases the dispersion process still further. Another advantage arising from the mode of action of colchicine is a concentration of the colchicine metaphases. Tissue culture is the method of choice for obtaining cell populations suitable for this technique. It was in this way that *Tjio* and *Levan*[8] in 1956 first determined the exact number of chromosomes in man as $2n=46$.

After culture the cells are fixed in a mixture of alcohol and acetic acid and are dropped onto cooled slides in this mixture. After spreading the cell suspension on the slide and drying off the fixation mixture, the chromosomes are stained with orcein. The metaphases can now be examined under a microscope.

The normal set of human chromosomes consists of 44 autosomes (22 pairs) and two X-chromosomes in the female and an X- and a Y-chromosome in the male. The chromosomes are classified schematically according to decreasing length, and are numbered from 1 to 22. The sex chromosomes are named as such. Figure 3 shows this classification for a female and a male metaphase.

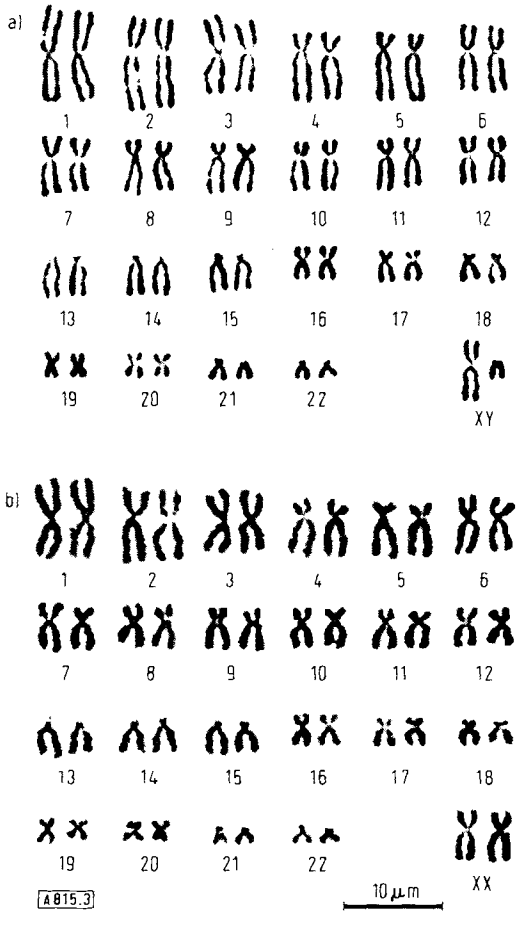


Fig. 3. Classified human metaphases: a) male, b) female. (Original from *Th. Lüers.*)

The substances to be tested for mutagenicity are added to the cell cultures at the desired concentrations some hours before processing. The metaphase chromosomes can then be examined for any damage.

A list of substances that have been found to be mutagenic *in vitro* in man is given in the table.

It is particularly important to note that chromosome mutations can be demonstrated not only after the action of mutagens *in vitro* but also after contamination *in vivo*, for example after chemotherapeutic treatment with cytostatics, after psychotropic drugs (*e.g.* LSD), and after inhaling polluted air (gasoline fumes). Such cases are marked with a cross in the "*in vivo*" column in the table.

2. Alkylating Agents[9–12]

Among the large number of mutagenic substances the alkylating compounds will be discussed here in greater detail. These compounds, which are considered to be some

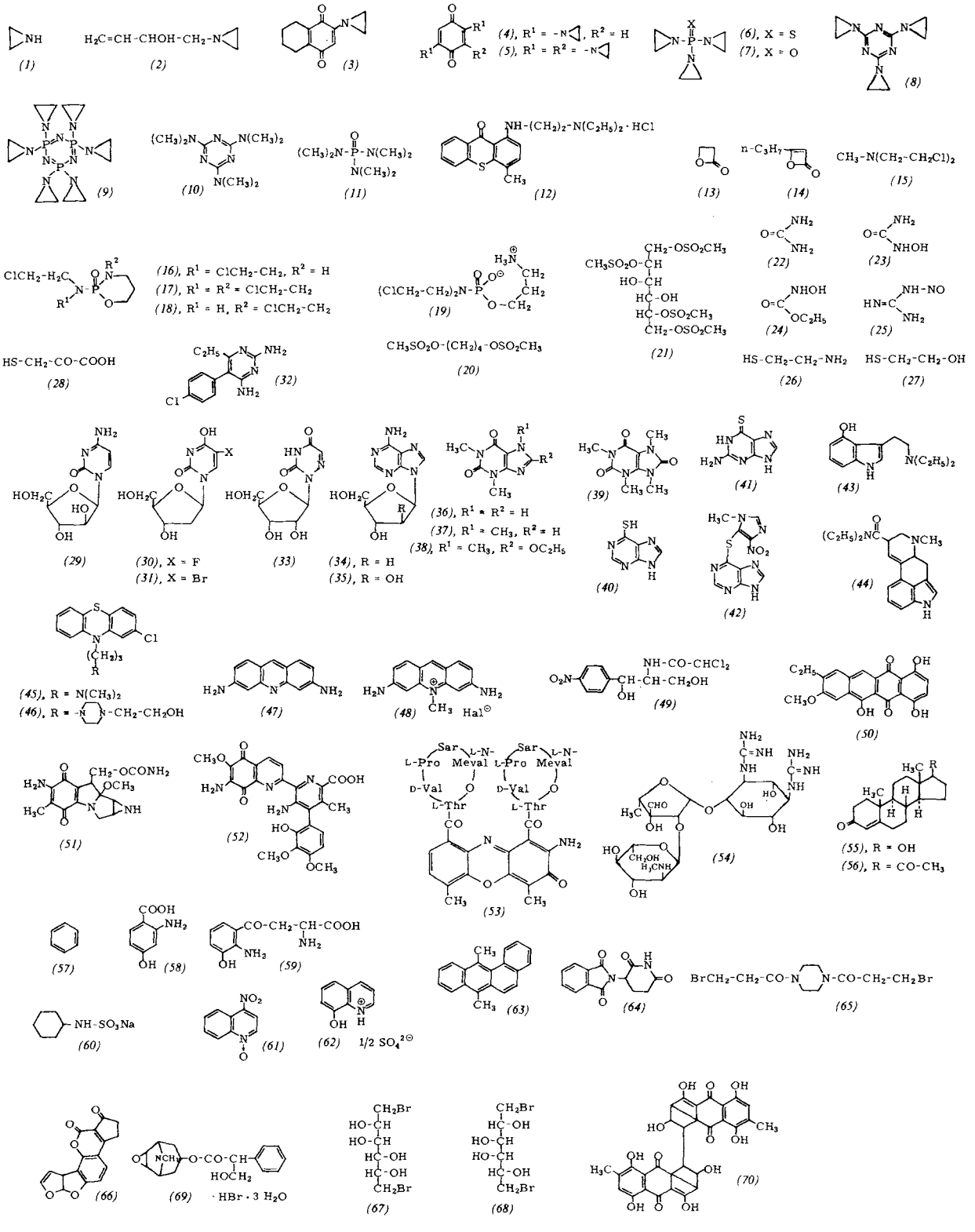


Table 1. Substances inducing aberrations in human chromosomes *in vitro* = after the action of the substance on cell cultures; *in vivo* = after ingestion or inhalation. (For a list of the formulas see page 306.)

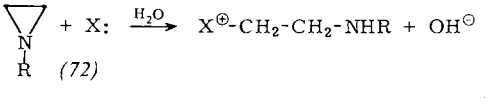
No. or formula	Name	Mutagen *in vitro*	Mutagen *in vivo*	Ref.
(1)	Aziridine, ethylenimine	+		[40]
(2)	1-Aziridino-3-buten-2-ol	+		[40b]
(3)	2-Aziridino-5,6,7,8-tetrahydro-1,4-naphthoquinone; A 137	+		[41]
(4)	2,5-Bis(aziridino)-1,4-benzoquinone; Quinone I	+		[39]
(5)	2,3,5-Tris(aziridino)-1,4-benzoquinone; Trenimon	+		[29, 42]
(6)	Tris(aziridino)thiophosphorane, Thio-TEPA, Tespa	+		[42]
(7)	Tris(aziridino)oxophosphorane; TEPA	+		[40b]
(8)	2,4,6-Tris(aziridino)-1,3,5-triazine; Triethylenemelamine, TEM	+		[42, 43]
(9)	2,4,6-Tris(aziridino)-1,3,5,2,4,6-triazatriphosphorine; Apholate	+		[40b]
(10)	Hexamethylmelamine; Hemel	+		[40b]
(11)	Hexamethylphosphoric acid triamide	+		[40b]
(12)	1-(2-Diethylaminoethylamino)-4-methylthioxanthone hydrochloride; Miracil D	+		[18]
(13)	β-Propiolactone	+		[44]
(14)	2-Hexenoic acid β-lactone	+		[44]
(15)	Bis(2-chloroethyl)methylamine, nitrogen mustard	+	+	[45]
(16)	2-[Bis(2-chloroethyl)amino]perhydro-1,3,2-oxazaphosphorine 2-oxide; Cyclophosphamide; Endoxan, Cytoxan	+		[46]
(17)	2-[Bis(2-chloroethyl)amino]-3-(2-chloroethyl)perhydro-1,3,2-oxazaphosphorine 2-oxide; Asta Z 4828	+		[47]
(18)	2-(2-Chloroethylamino)-3-(2-chloroethyl)perhydro-1,3,2-oxazaphosphorine 2-oxide; Asta Z 4942	+		[47]
(19)	*N*-Bis(2-chloroethyl)amidophosphoric acid 3-aminopropyl ester	+		[42]
(20)	Tetramethylene bis(methanesulfonate)	+		[48]
(21)	1,2,5,6-Tetrakis(methanesulfonyl)-D-mannitol	+		[49]
(22)	Urea	+		[50]
(23)	Hydroxyurea	+		[50]
(24)	*N*-Hydroxyurethane	+		[50]
(25)	*N*-Nitrosoguanidine	+		[51]
(26)	2-Aminoethanethiol	+		[52]
(27)	2-Mercaptoethanol	+		[52, 53]
(28)	3-Mercaptopyruvic acid	+		[54]
(29)	Cytosine arabinoside	+	+	[55]
(30)	5-Fluoro-2′-deoxyuridine	+		[42, 56]
(31)	5-Bromo-2′-deoxyuridine	+		[57]
(32)	2,4-Diamino-6-ethyl-5-*p*-chlorophenylpyrimidine; Pyrimethamine		+	[58]
(33)	6-Azauridine		+	[59]
(34)	2′-Deoxyuridine	+		[55d]
(35)	Adenine arabinoside	+		[60]
(36)	1,3-Dimethylxanthine, theophylline	+		[61]
(37)	1,3,7-Trimethylxanthine, caffeine	+		[61, 62]
(38)	8-Ethoxy-1,3,7-trimethylxanthine	+		[63]
(39)	1,3,7,9-Tetramethyluric acid	+		[63a]
(40)	6-Mercaptopurine	+	+	[45, 64]
(41)	6-Thioguanine	+		[57a]
(42)	6-(1-Methyl-4-nitro-5-imidazolylthio)purine; Azathioprin, Imuran	+	+	[65]
(43)	3-(2-Diethylaminoethyl)-4-hydroxyindole; CZ-74		+	[66]
(44)	Lysergic acid diethylamide, LSD	+	+	[67]
(45)	2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine; chlorpromazine		+	[67f]
(46)	2-Chloro-10-[3-(4-(2-hydroxyethyl)-piperazinyl)propyl]phenothiazine; perphenazine		+	[67f]
(47)	3,6-Diaminoacridine; Proflavine	+		[68]
(48)	3,6-Diamino-10-methylacridinium halide; acriflavine, Trypaflavine, Euflavine	+		[69]
(49)	Chloramphenicol	+		[70]
(50)	Daunomycin	+	+	[25, 71]
(51)	Mitomycin C	+		[72]
(52)	Streptonigrin	+		[73]
(53)	Actinomycin D	+		[68]
(54)	Streptomycin	+		[19]
A 649	Antibiotic of unknown constitution	+	+	[45]
(55)	Testosterone	+		[74]
(56)	Progesterone	+		[74]
O_3	Ozone	+		[75]
K_3AsO_3	Potassium arsenite	+		[50]
NH_2OH	Hydroxylamine	+		[57a, 57c]
(57)	Benzene		+	[76]
(58)	4-Hydroxyanthranilic acid	+		[77]
(59)	3-Hydroxykynurenine	+		[77]
(60)	Sodium cyclohexylamidosulfate; sodium cyclamate	+		[78]
(61)	4-Nitroquinoline-*N*-oxide	+		[79]
(62)	Chinosol	+		[80]
(63)	7,12-Dimethylbenz[*a*]anthracene	+		[81]
(64)	2-Phthalimidoglutarimide; Thalidomide, Contergan	+		[82]
(65)	1,4-Bis(3-bromopropionyl)piperazine	+	+	[83]
(66)	Aflatoxin B_1	+		[44]
(67)	1,6-Dibromomannitol	+		[84]
(68)	1,6-Dibromodulcitol	+		[84]
(69)	Scopolamine hydrobromide	+		[46d]
(70)	Luteoskyrin	+		[85]

of the most powerful mutagens known, are particularly used in therapy as cytostatics but they also play an important role as pesticides. In the textile industry they are needed in the production of dyestuffs as well as for the manufacture of fireproof and crease-resistant fabrics. It is particularly disquieting that they are also present in automobile exhaust fumes.

These compounds differ greatly in structure but they share the ability of transferring an alkyl residue to other atoms or molecules. In biologically active alkylating agents this alkyl residue is bound to the parent substance *via* an oxygen, nitrogen, or sulfur atom. An S_N2 reaction generally occurs in alkylation:

$$X: + RY \rightarrow X^+—R + Y^-:$$

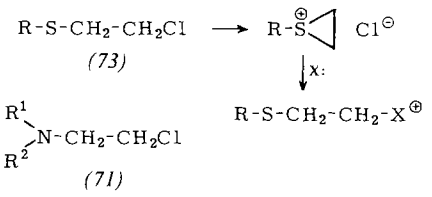
in which X is the nucleophilic agent and R is the alkyl residue. For example, the alkylation of the methanesulfonic ester $ROSO_2CH_3$ takes place in this way. In functional groups with a ring structure such as aziridines *(72)*, epoxides, and β-lactones the alkylation is associated with opening of the rings.



(72)

As regards the cytostatic effect of aziridine, it may be noted that the hydrolytic cleavage of the ring occurs four times as quickly at the typical pH of cancer cells (6.5) as at the pH of healthy cells (7.2)[131].

The sulfur and nitrogen mustards *(73)* and *(71)* form another highly active group. These have an alkylating effect only after forming a ring, and the rate of the reaction is thus determined by the relative rates of the two steps.



(73)

(71)

The *N*-nitroso compounds include the dialkylnitrosamines *(74)* and the acyl-alkylnitrosamides *(75)*. A characteristic of these substances is that they are inactive as such. These "transport forms" are converted by enzyme-induced and spontaneously occurring changes in the cell into forms with alkylating action.



(74) *(75)*

It is not only in the *N*-nitroso compounds that transport and active forms are differentiated. Another well known example of this is the nitrogen mustard derivative known as Endoxan or Cytoxan *(16)* (see Table 1), which is used in cancer therapy, and whose alkylating activity only develops after hydrolytic splitting in the liver.

The nucleophilic groups in the cell are primary to tertiary nitrogen atoms as well as OH, SH, and sulfide groups. Many reactions can thus take place between the alkylating agents and the biological material, but in these the alkylation of DNA is of central importance. Permanent changes in the DNA are produced by even the smallest quantities of alkylating agents. In isolated DNA it can be demonstrated that it is the bases in particular that are alkylated. Pyridine-type nitrogen atoms are attacked preferentially, which is understandable when one considers that the free pairs of electrons on such nitrogens are not incorporated into the conjugated electron system of the heterocycle. The introduction of an alkyl residue at this site thus does not result in any damage to the conjugated system but only in a small lowering of resonance energy. It is more difficult to understand, however, why the N-7 atom of guanine is alkylated most frequently, while the N-1 atom of this base and the N-3 and N-7 atoms of adenine are affected more rarely. Presumably these differences are due essentially to spatial effects in the double helix of DNA. *In vivo* the circumstances are even more complicated, but here too an N-7 alkylation of guanine can be demonstrated after treatment with tritiated β-propiolactone.

Besides the bases being attacked, certain alkylating agents, such as the nitrogen mustard *(15)*, primarily attack the phosphate groups. Part of the phosphate ester thus formed is broken down hydrolytically and liberates an alkyl radical which can then react with a base. This process and direct alkylation of the bases thus lead to the same result. Following the formation of an alkylguanine and hydrolytic breakdown of the base and deoxyribose compound, the guanine can be eliminated and thus result in a break in the polynucleotide chain.

The biological activity of alkylating compounds with several functional groups is greatly superior to that of alkylating agents carrying only one functional group. This can be attributed to the formation of cross-linkages. Such cross-links can bridge the sister strands of the DNA double helix or two molecules within the same strand of the double helix. Bridges between different double helices can be shown by electron microscopy. Cross-links between chromosomal proteins and the DNA must also be taken into consideration. The severe toxic effect of polyfunctional alkylating agents is probably due to these linkages, which hinder or prevent correct replication of the DNA.

The damage to the DNA caused by alkylation is repaired for the most part by enzyme action. Occasionally resulting mistakes in the repair process alter the native base sequence and are thus undoubtedly a source of point mutations. How alkylation results in changes in the chromosomes that can be observed under the light microscope is still largely unknown. It will only be possible to solve this problem when the structure of chromosomes in higher organisms has been clarified.

The results can certainly be best explained if one assumes that a single chromosome in the nucleus of a non-dividing cell (an interphase nucleus) consists of only one continuous DNA double helix which, in association with proteins, acts as a matrix for the formation of sister chromosomes in the synthesis phase of the cell cycle. In the C-metaphase these appear as two chromatids still attached to the kinetochore (cf. Fig. 2). The contraction of the chromosomes could be interpreted as a progressive folding of the DNA protein fibrils of each chromatid (the folded fiber model of chromosome structure)[14, 15]. If the breaks occurring in a DNA strand of an interphase chromosome as a result of alkylation are not repaired, a break occurs in the fibrils of one of the chromatids found after replication. This concept is also in agreement with the fact that defects are only found in the chromatids in the first metaphase after the introduction of an alkylating agent (in the previous interphase). These chromatid aberrations can be transformed into chromosome aberrations after a further mitosis, but this is generally not observed because of their lethal effect. To obtain a true picture of the pattern of damage in the chromosomes it is thus important to detect the first mitosis occurring after the introduction of the alkylating agent.

Some results obtained with these two test systems will be compared and discussed in the following sections.

2.1. Achromatic Lesions (AL)

Achromatic lesions appear very frequently in human chromosomes. These are color defects in the longitudinal structure of the chromatids, and are not breaks in the chromatid structure. The chromatid areas distal to the achromatic lesion are not separated from the proximal section (near the kinetochore). The lesions are probably repaired again in the synthesis phase following their induction[16].

Of particular importance is the question whether the achromatic lesions should be considered as equivalent to mutations. Comparative observations on the mutagenic efficacy of the thioxanthone derivative Miracil D *(12)* (see Table 1) on *Drosophila*[17] and human chromosomes[18] indicate that this question can be answered in the negative. In *Drosophila* Miracil D has almost no effect at all, except that the frequency of chromosome changes is increased above that in controls. After addition of Miracil D the testicular spirals of *Drosophila* are stained and so it could be determined that the substance had actually accumulated here and had not, for example, been metabolized after administration and then excreted without producing any effect.

In human chromosomes there were, in addition to some translocations, over 40% of achromatic lesions 24 hours after the introduction of 1×10^{-5} mole/ml. If these were equivalents of mutations then the frequency of the sex-linked lethals in *Drosophila* would have to be increased, especially as the test concentrations used were of the same order of magnitude.

Further help in throwing light on this problem has been provided by studies on the action of antibiotics which are not mutagenic to higher organisms, *i.e.* streptomycin *(54)* (see Table 1) and dihydrostreptomycin, on human chromosomes *in vitro*[19]. Whereas streptomycin induced almost 40% of achromatic lesions, dihydrostreptomycin was completely inactive. The frequency of all the other types of aberrations was not increased by either antibiotic, apart from quite sporadic translocations occurring equally after streptomycin and dihydrostreptomycin. These antibiotics differ among other things in that streptomycin is linked ten times more strongly to polyanions than is dihydrostreptomycin[20]. The achromatic lesions could arise by such nonspecific linkages to chromosomal polyanions.

2.2. Chromatid Breaks (B′)

Chromatid breaks are true ruptures in chromatids. In the anaphase following their induction the broken segment is left behind and can, at the most, arrive passively in one of the developing daughter cells. This type of damage thus leads to the loss of terminal sections (deletions).

The loss of terminal sections occurs only rarely in man spontaneously (in about one out of 100,000 births) and causes very severe malformations. The loss of a section on the short arm of chromosome no. 5 results in the development of the cat cry syndrome (cri-du-chat syndrome)[21], named after the cat-like cries of the children, who also have many malformations.

2.3. Isochromatid Breaks (B″)

Isochromatid breaks form another type of aberration which can be detected in the cytogenetic test. This type consists of two breaks which occur at morphologically homologous sites on two sister chromatids. They lead to the formation of two chromatid sections without kinetochores and of a residual chromosome. An isochromatid break results in the loss of chromatid sections in both daughter cells.

Figure 4a shows a metaphase with achromatic lesions and chromatid and isochromatid breaks in addition to chromatid translocations. The damaged chromosomes are illustrated separately in Figure 4b.
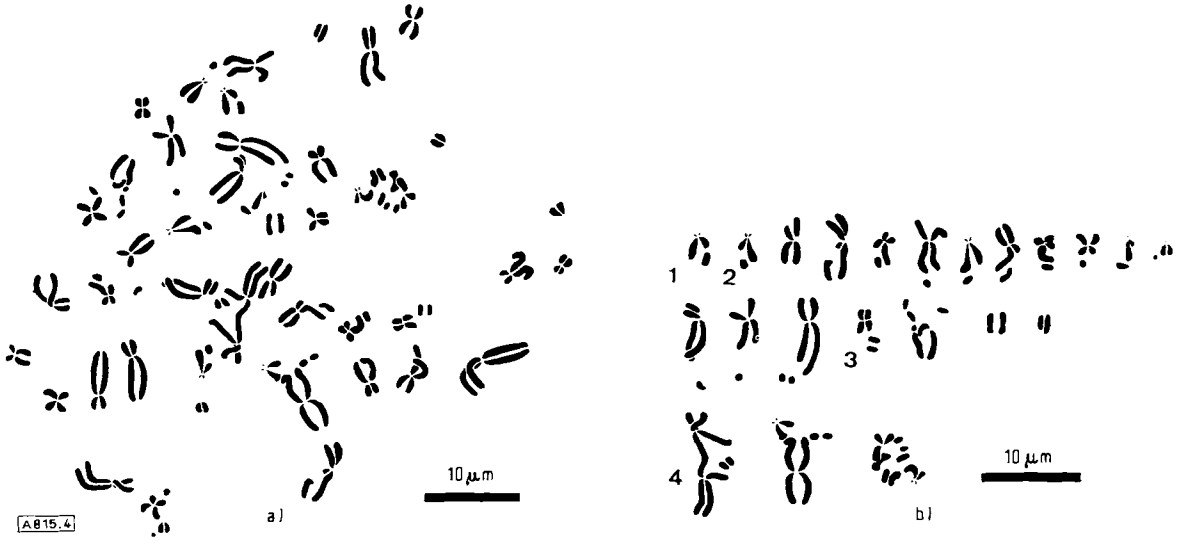


Fig. 4. a) Metaphase with chromosome damage resulting from 32 hours' exposure to 0.02 µg/ml of Quinone I *(4)*. b) Composition of the damaged chromosomes. 1 = achromatic lesion; 2 = chromatid breaks; 3 = isochromatid breaks; 4 = chromatid translocations (after [39]).

2.4. Chromatid Translocations (RB′)

Chromatid translocations are the most easily recognized and the most obvious equivalents of mutations. They are the result of repair processes in which unrelated fragments

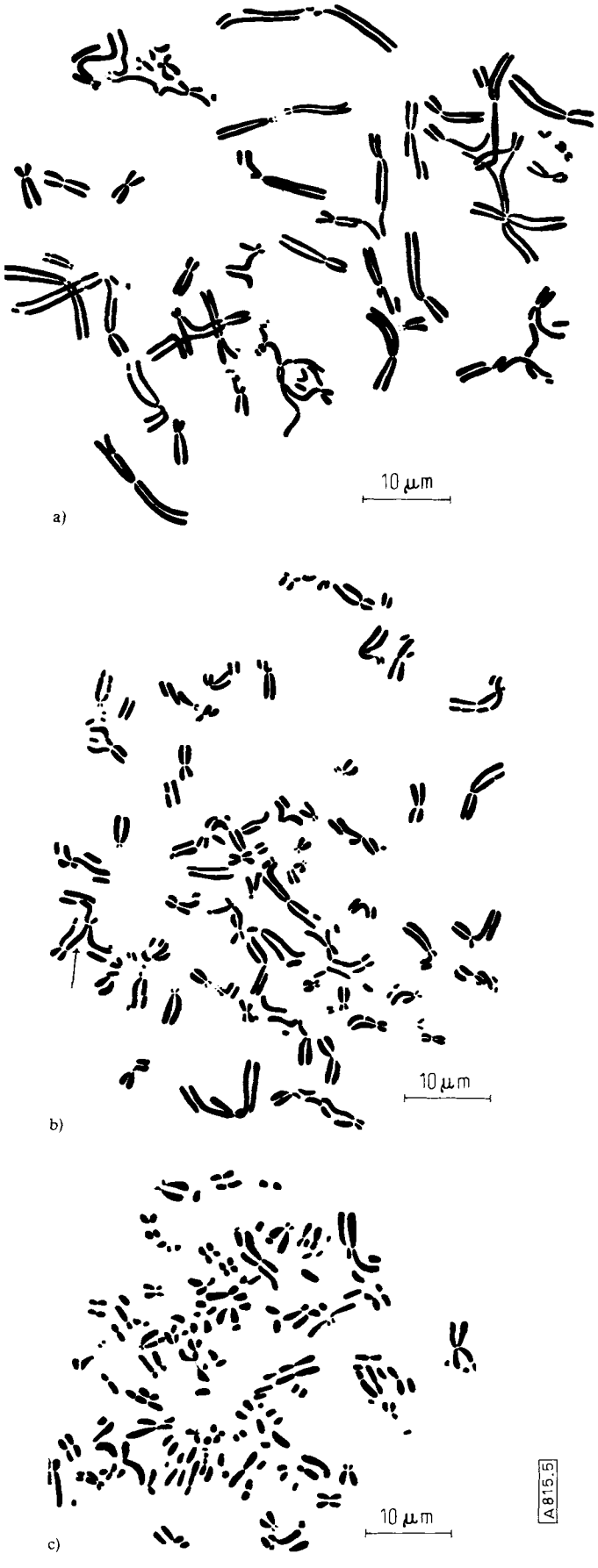


Fig. 5. Metaphases with damage of varying severity as a result of 24 hours' exposure to 5.0×10^{-7} mole/ml of Trenimon *(5)*. a) Numerous chromatid translocations; b) in addition to numerous breaks there is still only one chromatid translocation (arrow); c) completely disintegrated metaphase (pulverization) without any chromatid translocations (after [29]).

of different chromatids have been joined together. These translocations generally have the typical shape of a cross.

RB′ figures differ in the way they are jointed together; in some the kinetochores are not united with one another (symmetrical RB′), while in others the kinetochores are joined by chromatid bridges (asymmetric RB′), which in the following anaphase extend between the kinetochores migrating to the poles.

Translocations can be regarded as a visible expression of the repair processes taking place in the cell. The very severely disordered metaphases, which occasionally appear without any translocations, indicate a breakdown of the repair system in these cells. Figures 5a–5c show transitions ranging from severely disordered metaphases with translocations to those which appear completely "pulverized".

The intercellular distribution of the translocations and breaks also makes it possible to draw conclusions concerning repair processes in the cell[22]. If one assumes a random distribution of the primary defects in the cells investigated, then the chromatid breaks and translocations in each cell must fall into a *Poisson* distribution. However,

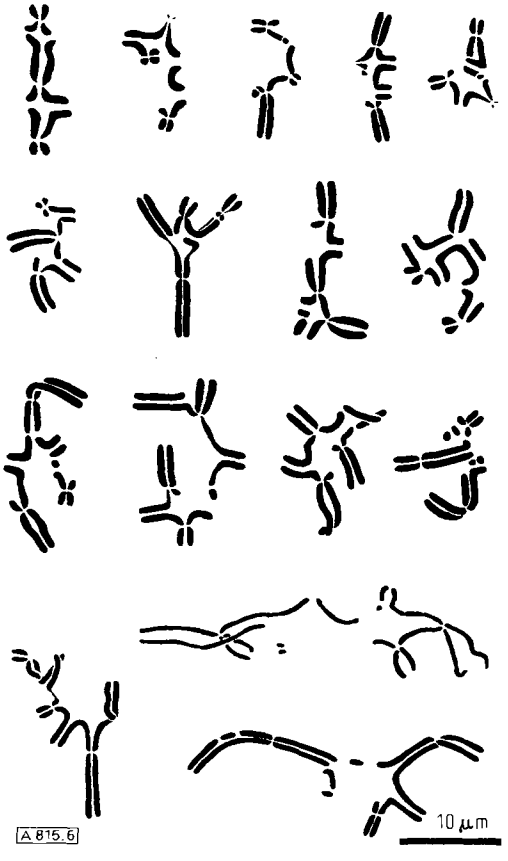


Fig. 6. Chromatid translocations (RB′) from three chromosomes after 24 and 32 hours of exposure to Quinone I *(4)* (after [39]).

after treatment with Quinone I *(4)* (see Table 1) there were too many cells in the 0-class, *i.e.* without chromosome aberrations; these are probably cells in which all the defects had been restricted.

Another question is the period within which healing of potential translocation-producing breaks can occur. X-ray experiments on human lymphocytes have given a period of 60–90 minutes[23].

The number of translocations formed can be reduced by inhibitors both of DNA and of protein synthesis[24–27], which indicates that such syntheses participate in the formation of translocations.

In addition to translocations involving two chromatids, translocations occur in mutation experiments in which more than two elements take part. Figure 6 gives some examples of translocations between three chromosomes.

In man, spontaneous translocations occur just as rarely as deletions. A translocation between chromosomes 13 and 21 leads to the formation of a new chromosome, whose short arm corresponds to chromosome no. 21 and whose long arm corresponds to chromosome no. 13. The short arms of the two affected chromosomes are lost during the translocation and appear to be of no genetic significance. The carriers of this translocation are phenotypically normal, but have only 45 chromosomes. Figure 7a shows the chromosome complement of a female carrier of this trans-

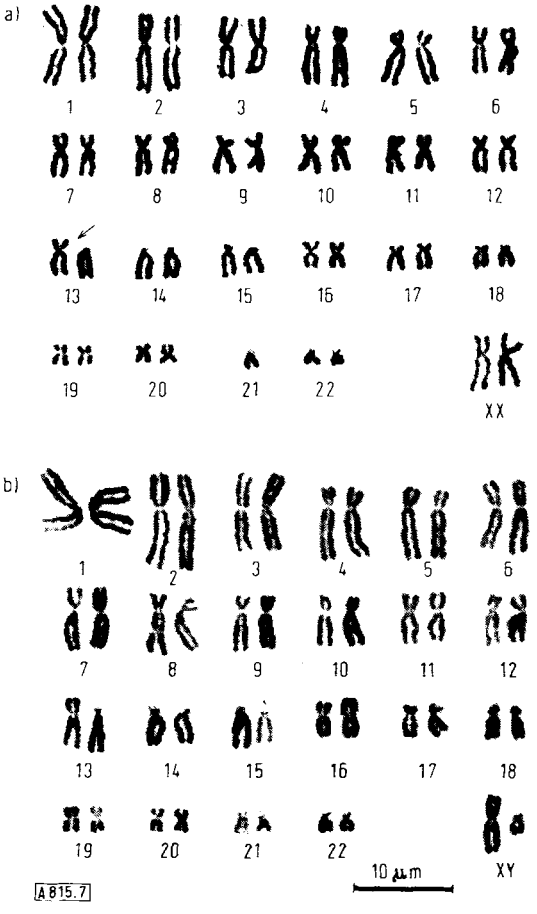


Fig. 7. Classified human metaphases with translocation chromosome 13/21 (arrow). a) Balanced state (45 chromosomes); b) combined with trisomy 21 (translocation mongolism, 46 chromosomes). (Original from *Th. Lüers.*)

location. If the chromosome no. 21 and also the translocation chromosome attain one oocyte, then after fertilization with a normal spermatozoon there appears an organism with $2n = 46$ chromosomes, but one that has three times the gene dose for chromosome no. 21 and is thus affected with Down's syndrome (translocation mongolism)[28]. Figure 7b shows the chromosome complement of a male translocation mongol.

3. Dose-effect Relationships

All the aberration types mentioned (AL, B', B'', and RB') increase in frequency with increasing dose of the mutagen unter test. Figure 8 shows such dose-effect relations for the

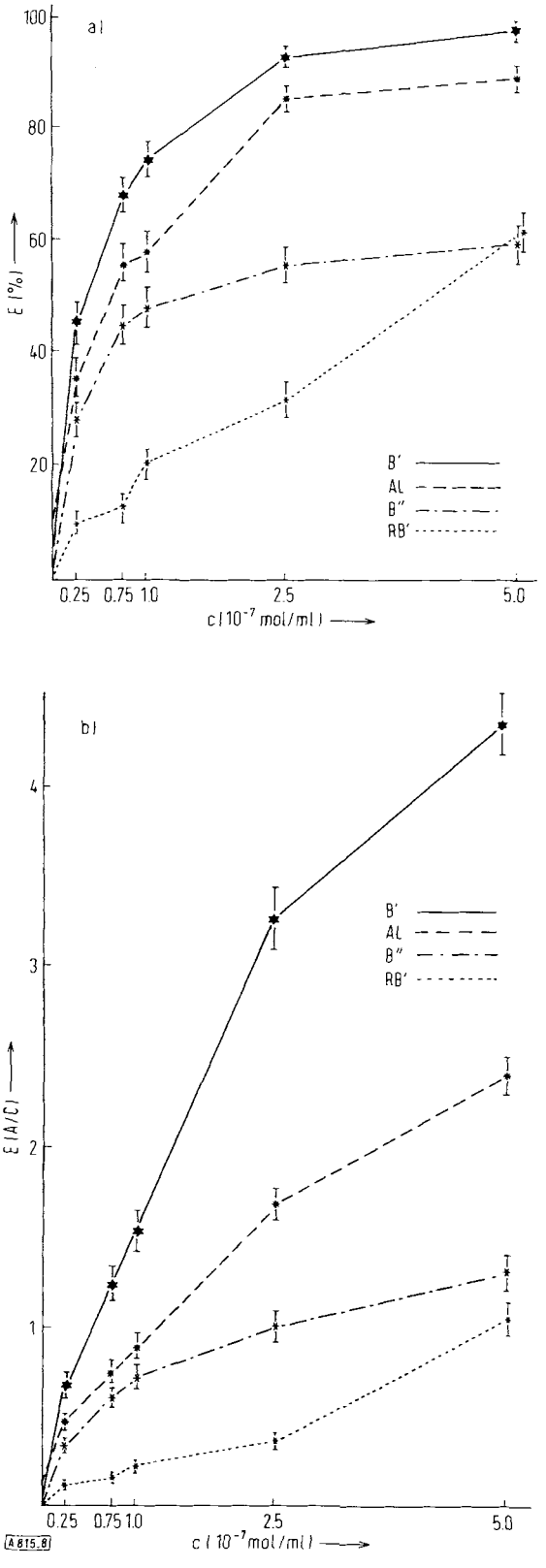


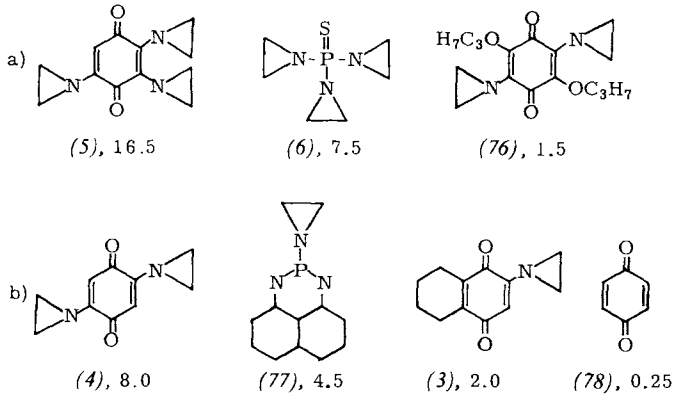
Fig. 8. Dose-effect relationships for achromatic lesions (AL), chromatid breaks (B'), isochromatid breaks (B''), and chromatid translocations (RB') as a result of 24 hours' exposure to Trenimon *(5)*. a) The effect (E) in percent; b) the effect in aberrations per cell (A/C) (after [29]).

alkylating agent Trenimon *(5)*[29] (see Table 1). Dose-effect relationships are also shown in recessive lethal mutations of *Drosophila*, for example after the administration of increasing doses of triethylenemelamine *(8)*[30] and nitrogen mustard derivatives[31].

4. Chemical Constitution and Mutagenic Action

The connection between chemical constitution and mutagenic action will be discussed on the examples of some aziridines.

As regards the induction of recessive lethal mutations there is a positive correlation with the number of aziridine groups per molecule[32]. Thus, the trifunctional Trenimon *(5)* is 10 times more active than the bifunctional E 39 *(76)*, while the bifunctional Quinone I *(4)* is 3.5 times as mutagenic as the monofunctional A 137 *(3)* (Scheme 1). However, the parent substance of an alkylating agent also has an effect

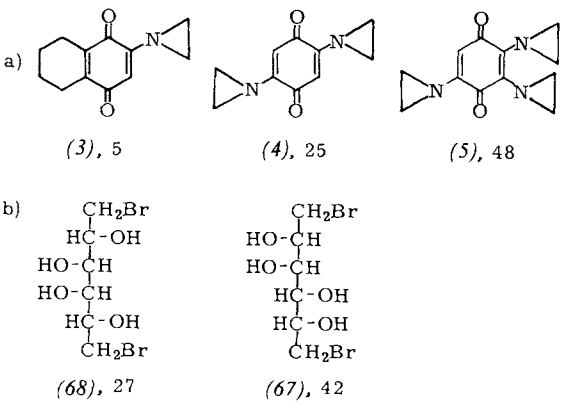


Scheme 1. Frequency of recessive lethal mutations in the X-chromosome of *Drosophila melanogaster* as a result of three days' feeding of a) 2.3×10^{-4}% solutions of Trenimon *(5)*, thio-TEPA *(6)*, and E 39 *(76)* (2,5-bis(aziridino)-3,6-*n*-propoxy-1,4-benzoquinone) and of b) 2.3×10^{-2}% solutions of quinone I *(4)*, A 140 (2-aziridino-1,3-diaza-2-phosphaperhydrophenalene) *(77)*, A 137 *(3)*, and *p*-quinone *(78)*. The numbers under the formulas give the frequency (%) (according to values from [32]).

on its mutagenic activity. Trenimon *(5)* has twice the activity of Thio-TEPA *(6)*, although both substances are trifunctional aziridines.

The number of mutations occuring does not show a simple relationship with the number of reactive groups. An *in vitro* study on human chromosomes to compare the efficacy of 1×10^{-6} mole/ml of A 137 *(3)* (monofunctional), 0.5×10^{-6} mole/ml of Quinone I *(4)* (bifunctional), and 0.33×10^{-6} mole/ml of Trenimon *(5)* (trifunctional) showed that, in spite of the same number of aziridine groups per culture, Trenimon was considerably more effective than Quinone I, and the mutagenic effect of the latter was clearly superior to that of A 137[33].

Scheme 2 shows the results of this experiment with reference to the translocations. An effect is produced here by cross-linking, which can only occur with the polyfunctional and not the monofunctional alkylating agents.



Scheme 2. Frequency of chromatid translocations in human chromosomes as a result of a) 24 hours' exposure to 1×10^{-6} mole/ml of A 137 *(3)*, 0.5×10^{-6} mole/ml of Quinone I *(4)*, and 0.33×10^{-6} mole/ml of Trenimon *(5)* (according to values from [32]) and b) 40 hours' exposure to 1×10^{-5} mole/ml of dibromodulcitol *(68)* and dibromomannitol *(67)*. The numbers under the formulas give the frequency (%).

The difference in the efficacy of dibromodulcitol *(68)* and dibromomannitol *(67)* in inducing translocations (RB') indicates that the spatial structure of a compound has an effect on its mutagenic action (Scheme 2).

5. Localization of the Mutations

Using a very large amount of material, *Belitz* investigated the distribution of spontaneous recessive lethal factors and of those induced by Quinone I *(4)* and triethylenemelamine *(8)* on the genetic map of the X-chromosome in *Drosophila*[34]. The spontaneous mutations were most frequent in the distal section (32.4%), with a minimum (9.8%) in the proximal section near the kinetochore of the affected chromosome. After treatment with Quinone I, 14.4% of the lethal factors were found in the distal section, against 19.1% in the kinetochore region. These differences could be confirmed statistically. A characteristic distribution pattern is also shown by mutations induced by triethylenemelamine *(8)* (distal 20.5%, proximal 23.2%). Mutations thus clearly occur more frequently in certain regions of the X-chromosome.

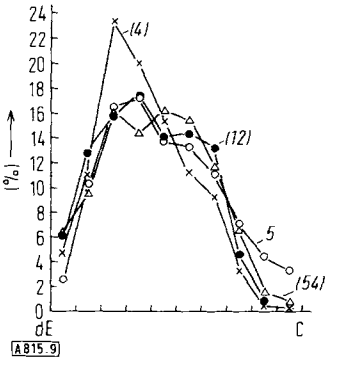


Fig. 9. Distribution of achromatic lesions and chromatid breaks in ten relatively equal sections of all the chromosomes of the human karyotype after exposure to Quinone I *(4)*, Trenimon *(5)*, Miracil D *(12)*, and streptomycin *(54)*, dE = distal end; C = kinetochore (according to values from [19, 29, 35, 36]).

The aberrations in human chromosomes are also not distributed at random. A similar distribution pattern is given by achromatic lesions (AL) and breaks (B') on ten sections of relatively the same length from all the chromosome arms after treatment with Trenimon *(5)* (AL+B')[29], Quinone I *(4)* (AL+B')[35], Miracil D *(12)* (AL+B')[36], and streptomycin *(54)* (AL)[19] (Fig. 9). The aberrations occur most frequently in the central region and decline greatly toward the distal end and the kinetochore region. Whereas in *Drosophila* the mutations are mainly concentrated at the distal end and in the kinetochore region, the achromatic lesions and chromatid breaks have precisely the opposite distribution in human chromosomes.

6. Concluding Remarks

We have attempted to give a brief and illustrative insight into chemogenetics on the basis of some results obtained with a genetic test system *(Drosophila)* and a cytological test system (cultured human cells). Today work on mutation occupies a very important position within genetics and is closely associated with other lines of research. Whereas the processes which lead to gene mutations are in principle well known, we still know relatively little about the processes which give rise to chromatid or chromosome aberrations[37]. Study of the repair processes is also part of the field of mutation research.

The techniques for producing mutations are extremely useful in other fields, for example developmental genetics, which can lead to significant inferences concerning the importance of a normal allele in the development of an individual from the abnormal action or lack of function of a mutated allele. On a larger scale, the population geneticist uses mutagenic agents to increase the genetic variation in artificial populations or to observe what happens to populations under increased mutation pressure.

The practical importance of mutation research is just as great as its scientific significance. Mutations are produced on a large scale in the breeding of cultivated plants and tested for their suitability for increasing quality and yield.

As is well known, most new mutations have an unfavorable effect. An especially important task for mutation research is developing from the constant contamination of our environment with a large number of materials whose genetic effects are known insufficiently or not at all. The increasing pollution due to the use of substances such as food additives, therapeutic agents, narcotics, contraceptives, and pesticides, as well as pollution of the oceans and the atmosphere, is rapidly becoming one of the most pressing problems of our time. The danger of such chemicals producing mutations in man is definitely greater than the risk of mutations caused by radiation.

Investigations on the possible mutagenic effect of such substances are thus of special importance. When a substance is recognized to be mutagenic it should be treated with extreme caution; whenever possible, it should be banned completely from our environment, as is shortly to happen in the United States with cyclamates, which are suspected of being mutagenic and carcinogenic[38].

While acute biological effects, such as signs of poisoning, are recognized immediately and the blame can generally be placed squarely on the toxic agent responsible, there is a much longer period between the mutation process and the manifestation of a genetically induced defect. Dominant mutations, which constitute the great majority of chromosome mutations, are as a rule lethal, and in man they probably lead mainly to early abortions. They are therefore not recognized as mutations. Dominant genetic defects leading to malformations occur relatively rarely among the whole range of mutations, and recessive autosomal hereditary changes can only be revealed in later generations.

As induced mutations do not differ qualitatively from natural (spontaneous) mutations, it is only possible to demonstrate an induced mutation statistically. However, if one were to wait for statistical proof of an increased incidence of mutations in man as a result of contamination with mutagens, then the damage already caused could be incalculable.

The only possible way of protecting mankind from mutagenic substances is the laboratory testing of all chemicals before they reach our environment. This is a gigantic task when it is realized that about 30,000 new chemical compounds are developed every year. A particular difficulty standing in the way of this undertaking is that of raising funds to prevent dangers whose extent is not immediately obvious to the general public.

In view of all this, the founding by American geneticists of an Environmental Mutagen Society (EMS), a European section of which was set up recently, is highly welcome. The German Research Association maintains a "Central Laboratory for Mutagenicity Testing" at Freiburg-im-Breisgau, where chemicals are tested for their possible mutagenic effects in close cooperation with the chemical industry.

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Sulfinato Complexes

By Günther Vitzthum and Ekkehard Lindner[*]

Sulfinatometal complexes exhibit unusual features in their structure, preparation, and use, and have attracted rapidly growing interest. Their structures are determined by the ability of the RSO_2^- group both to act as a monodentate ligand (sulfinato-S or sulfinato-O) and to add to coordination centers as a bidentate ligand, either intramolecularly or intermolecularly, via the two oxygens atoms (sulfinato-O,O') or via the sulfur atom and one of the oxygens (sulfinato-O,S).

1. Introduction

In 1858, *Hobson*[1] published an article "On the Action of Sulfurous Acid on Zinc Methyl". When dry SO_2 is passed into a solution of $(CH_3)_2Zn$ in ether, a colorless precipitate is formed; this was described as the "zinc salt of methylodithionic acid". However, the analytical data reported and the manner of preparation (insertion of SO_2) indicate that it is bis(methanesulfinato)zinc, the structure of which was not elucidated until 110 years later[2, 3]. The behavior of $(C_2H_5)_4Sn$ toward SO_2 was investigated by *Frankland* and *Lawrance*[4] in 1879. *Peters*[5] later allowed arenesulfinic acids to react with Hg^{II} salts. This reaction is used for the preparation of homogeneous mercury sulfinates having definite compositions[6]. Since 1937, aromatic sulfinic acids have been used in analytical chemistry for the quantitative determination of transition metals[7–9].

Wide industrial application of sulfinic acids followed from the observation[10, 11] that unsaturated organic systems containing sulfinic acids rapidly polymerize in the presence of transition metal salts[12–17]. Highly reflective nickel coatings can be deposited electrolytically from baths containing nickel salts of sulfinic acids[18]. Finally the bactericidal effect of benzenesulfinatosilver can be used for the production of antiseptic soaps[19].

Though numerous investigations on sulfinato complexes had been reported by 1964, little was known about their structure and bonding. The increased attention that has been devoted to these problems during the last six years is due in no small measure to the variety of ways in which the RSO_2^- ligands can be bonded to coordination centers.

2. Problems of Structure and Bonding

2.1. Possibilities for the Coordination of the RSO_2^- Ligand

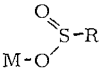
The bonding of a potential polydentate ligand such as carboxylate[20], nitrate[21], carbonate[20], sulfate[20, 22], sulfinate[23] or sulfolan[24] can very often be determined by IR spectroscopic investigations, since the corresponding CO_2, NO_3, CO_3, SO_4, and SO_2 stretching vibrations change on coordination. The stronger the bond between the metal and the ligand, the greater is the shift of the element-oxygen absorption bands to lower or higher frequencies. For oxo anions with D_{3h} (NO_3^-, CO_3^{2-}) or T_d (SO_4^{2-}) symmetry, we find frequency splittings of degenerate vibrations and the additional appearance of originally forbidden bands because of decreased symmetry. The greater the number of bonds formed between a polydentate ligand and a metal, the greater is the splitting of the degenerate element-oxygen absorptions.

For a sulfinato complex having the general, simplified composition RSO_2M (R = organic residue, M = central ion) there are four possibilities for bonding the RSO_2^- ligand to coordination centers[23]:

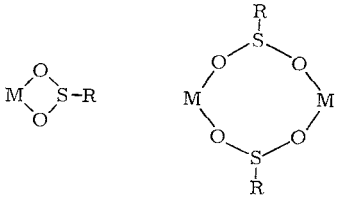
1. *Sulfinato-S complex*; the central ion is linked directly to the sulfur:



2. *Sulfinato-O complex*; the RSO_2^- group is linked to the coordination center by one oxygen atom:

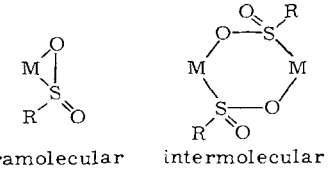


3. *Sulfinato-O,O' complex*; the RSO_2^- ligand is coordinated to the central ion *via* both O atoms:



intramolecular intermolecular

4. *Sulfinato-O,S complex*; the RSO_2^- ligand can be coordinated *via* oxygen and sulfur:



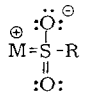
intramolecular intermolecular

The frequencies of $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ show whether a complex is of the sulfinato-*S* or sulfinato-*O* type, and their

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difference shows whether one or both O atoms are bonded to the central ion.

For a sulfinato-*S* complex, $\nu_{as}(SO_2)$ absorbs in the range 1250—1100 cm^{-1}, and $\nu_s(SO_2)$ between 1100 and 1000 cm^{-1}. In comparison with sulfones[25], the bands are shifted by 150—100 cm^{-1} to lower wave numbers, evidently because of a strong π interaction between the metal and the sulfur[26,27]:



In the sulfinato-*O* type, the "free" S—O stretching vibration absorbs between about 1100 and 1050 cm^{-1}, whereas ν_{as}(S—O—M) is shifted to lower frequencies in comparison with the longer-wave $\nu(SO_2)$ band of the free sulfinate ion; the frequency difference here is usually 100—200 wave numbers. The structures of two sulfinato-*O* complexes, *i.e.* $(p\text{-}CH_3C_6H_4SO_2)_2Cu(OH_2)_4$[28] and

$[\pi\text{-}C_5H_5Fe(CO)_2]_2Sn(O_2SC_6H_5)_2$[29,30],

have so far been established by X-ray studies. Only for the copper compound are the IR data[31] in conflict with the type of bonding found in the structural investigation.

For a sulfinato-*O,O'* complex, $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ are shifted to longer wavelengths in comparison with the SO_2 stretching vibrations of the free anion, with a frequency difference of 10 to 80 cm^{-1}.

The most problematic is doubtless the last type of linkage mentioned, *i.e.* the sulfinato-*O,S* type, which is relatively rare[32,33]. The intramolecular arrangement should be unlikely in any case because of excessive ring strain.

The dependence of the frequency difference between $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ on the angle is illustrated by the following example. In the *p*-dimethylaminobenzenesulfonylium ion[34], the sulfur is certainly sp^2-hybridized, and the O—S—O angle is therefore approximately 120°. Whereas the frequency difference here is 223 cm^{-1}, it decreases to only 66 cm^{-1} for the sulfinato-*O,O'* complex $[p\text{-}CH_3C_6H_4SO_2Ni(phen)_2]Cl$[32]. The difference becomes understandable when one considers that the O—S—O angle must be distorted because of the electrostatic influence of the Ni^{2+} ion on the sulfinate ion. Similar arguments are valid for the sulfolan coordination[24]. As the O—S—O angle becomes smaller, the vibrations of the sulfolan molecule should change, since the coupling of the symmetrical SO_2 stretching vibration depends mainly on the O—S—O angle[35].

2.2. Criteria for the Formation of Sulfinato-*S* and Sulfinato-*O* Complexes

The sulfinate ion can act in two ways as an electron donor, *i.e.* as a "soft" donor[36–38] *via* the S atom or as a "hard" donor *via* one or both O atoms. This allows the specific preparation of sulfinato-*S* or sulfinato-*O* complexes, according to whether a "soft" or a "hard" coordination center is offered to the RSO_2^- group.

2.2.1. Sulfinato-*S* Complexes

To prepare a sulfinato-*S* complex, the central ion must have a soft (b[38]) character. This requires the lowest possible oxidation number, a low positive charge, a large ionic radius, occupied outer orbitals, and high polarizability.

The other ligands bonded to the coordination center besides RSO_2^- must have primarily π-acceptor as well as donor properties. Because of its energetically favorable, empty d orbitals, sulfur itself is suitable for the acceptance of the negative charge of the central ion *via* a (d-d)π bond.

By suitable choice of ligands, it is possible to induce a soft character in a metal ion that is hard by nature. Typical examples of this are found among the sulfinato-*S* complexes of Co^{III}: $[Co(SO_2R)(CN)_5]^{3-}$[39], RSO_2Co(salen) (salen = *N,N'*-ethylenebis(salicylideneiminato))[40], and $[RSO_2\text{-}Co(dmgH)_2py]$ (dmgH = dimethylglyoximato)[41].

2.2.2. Sulfinato-*O* Complexes

The conditions for obtaining a sulfinato-*O* complex are hard character of the central ion, *i.e.* higher oxidation number, higher effective charge, small ionic radius, low polarizability, and low oxidizability. The ligands coordinated besides RSO_2^- must be hard, *i.e.* they must have mainly donor properties.

A sulfinato-*S* complex may be converted into a sulfinato-*O* complex by ligand exchange or addition reactions[27,31]:

$$\underset{\text{sulfinato-}S}{CF_3SO_2Fe(CO)_4Cl} + 2\,THF \rightarrow \underset{\text{sulfinato-}O,O'}{CF_3SO_2Fe(THF)_2Cl} + 4\,CO \quad (1)$$

$$\underset{\text{sulfinato-}S}{(RSO_2)_2Hg} + 2\,H_2O \rightarrow \underset{\text{sulfinato-}O,O'}{(RSO_2)_2Hg(OH_2)_2} \quad (2)$$

Thus hard ligands without π-acceptor properties cause rearrangement of the RSO_2^- group such that it becomes bonded to the central ion *via* the hard oxygen.

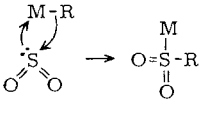
3. Preparation

The fundamental routes to obtain sulfinato complexes are as follows:

(a) *Insertion of SO_2 into the metal-carbon bond of organometallic compounds:*

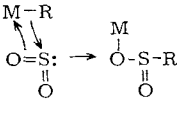
$$R\text{—}M + SO_2 \rightarrow RSO_2M \quad (3)$$

Investigations on the reaction mechanism[42–48] point to an electrophilic cleavage of the metal-carbon bond. Depending on whether SO_2 attacks the central ion nucleophilically *via* sulfur or oxygen, the result is a sulfinato-*S* [eq. (4)] or a sulfinato-*O* complex [eq. (5)].



(4)

S_Ei

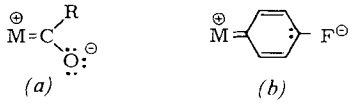


(5)

Transition metals in low oxidation states (soft character; cf. Sections 2.2.1 and 3.1.1) and some Hg compounds show a preference for path (4). With metals of hard character, such as Zn, Al, Ga, In, Tl, Sn, and Pb, on the other hand, the SO_2-insertion takes place in accordance with eq. (5). Except in the cases of organotin and organolead compounds, the cleavage of the metal-carbon bond by SO_2 becomes more difficult in the following order[26,48]:

$$CH_3 \sim C_2H_5 \gg C_6H_5 \sim CH_2C_6H_5$$

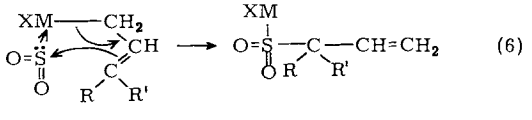
Acyl, perfluoroalkyl, and perfluoroaryl derivatives of transition metals do not react with SO_2[26]. This is traced back to a strengthened M—C bond as a result of significant contributions from the resonance structures *(a)* and *(b)*[49,50].



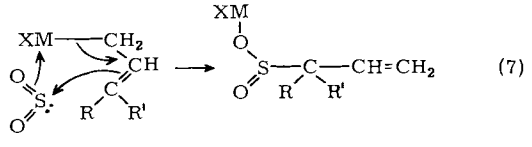
(a) *(b)*

Moreover, SO_2 is inserted preferentially into the *p*-tolylmercury bond of C_6H_5—Hg—$C_6H_4CH_3$; no reaction is observed with C_6H_5—Hg—Cl, $(C_6F_5)_2Hg$, or $(C_6Cl_5)_2Hg$, which have been found to be particularly resistant to electrophilic cleavage of the C—Hg bond[51]. These observations agree with the mechanisms given above [S_Ei; eq. (4), (5)].

Important information concerning the course of the reaction was obtained from the action of SO_2 on 2-alkenylmetal, allenylmetal, and 2-alkynylmetal compounds:

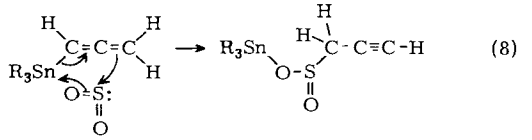


(6)

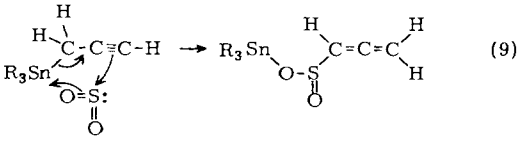


(7)

There is no doubt that reaction path (6) is favored in the case of $(CO)_5MCH_2CH{=}CRR'$ (M = Mn, R = H and CH_3, R' = CH_3; M = Re, R = R' = CH_3)[42,43]. As was shown by *Kitching et al.*[45–47], however, the insertion of SO_2 in allylstannanes (M = Sn, X = R_3) proceeds in accordance with eq. (7).



(8)



(9)

The examples (7)—(9) show that the insertion of SO_2 into 2-alkenyltin, allenyltin, and 2-alkynyltin derivatives is accompanied by rearrangement of these groups to form the alternative 2-alkenyl, 2-alkynyl, and allenyl structures respectively. Mechanisms as shown in eq. (6)—(9) may be described as S_Ei' cleavages[47]. The greatly increased reaction rates with alkenyltin, allenyltin, and alkynyltin derivatives are generally in agreement with the results of electrophilic cleavage in these organometallic systems.

The reasons for the complete absence of an S_E component of this insertion in allenetin compounds are not clear. The true reaction order with respect to SO_2 is probably greater than one, owing to donor-acceptor interactions with the metal or the unsaturated centers.

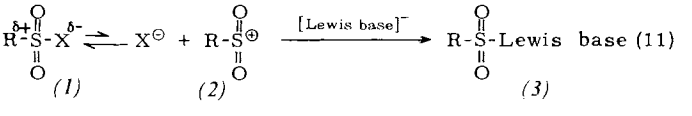
A well-established relation exists between the electrophilic cleavage of a C—Sn and of a C—Pb bond, the latter bond being more reactive. *Kitching* and *Fong*[48] found no evidence of an S_Ei' mechanism [eq. (7)] in the case of lead, since even the 2-butenyllead species are very unstable. However, the very fast reaction of the allyl complexes in comparison with the phenyl derivatives makes any other reaction path improbable.

(b) *Reaction of sulfonyl chlorides and sulfonic anhydrides with organometallic Lewis bases or neutral carbonylmetal compounds:*

$$RSO_2X + [\text{Lewis base}]^- \xrightarrow[THF]{-80\,^\circ C} RSO_2 - [\text{Lewis base}] + X^- \quad (10)$$

(R = CF_3, *p*-$CH_3C_6H_4$; X = Cl, *p*-$CH_3C_6H_4SO_3$; [Lewis base]$^-$ = $[Mn(CO)_5]^-$[52,53], $[Re(CO)_5]^-$[27], $[\pi\text{-}C_5H_5Fe(CO)_2]^-$[27,53], $[Co(CO)_3P(C_6H_5)_3]^-$[27,53]).

When a nucleophilic agent [Lewis base]$^-$ dissolved in a polar medium approaches the acyl halide or anhydride, the reaction [eq. (11)] probably proceeds by heterolysis *via* a transition state *(1)* to give the limiting form *(2)*. The intermediate cation *(2)* can then react with the nucleophile to form the derivative *(3)*, the heterolysis being the rate-determining step[53,54].



(1) *(2)* *(3)* (11)

The course of this reaction may therefore be compared with the behavior of aliphatic and aromatic acyl halides[54] or perfluorinated acid anhydrides[55] toward carbonylmetalates.

The action of organosulfonyl chlorides on mononuclear carbonylmetal compounds of the triads of groups V[56], VI[56], and VIII[27] leads, when R is electronegative (CF_3), to organosulfinato-*O,O'*-metal chlorides with bivalent metal:

$$RSO_2Cl + M(CO)_n \xrightarrow[n\text{-heptane}]{-20\,^\circ C/120\,^\circ C} RSO_2M(CO)_4Cl + (n\text{-}4)CO \quad (12)$$

(4)

$$(4) \xrightarrow[THF]{20\,^\circ C} RSO_2MCl + 4\,CO \quad (13)$$

(R = CF_3; M = V, Cr, Mo, W, Fe, Ni)

The reactions proceed *via* the more or less unstable intermediates (4).

With more electropositive R (*p*-$CH_3C_6H_4$), the products are organosulfinato-*O,O'*-metal chlorides with bivalent (Ni)

or trivalent metal (Fe), depending on the oxidizability of the carbonylmetal component[56]:

$$4\,RSO_2Cl + 2\,Fe(CO)_5 \xrightarrow[THF]{20^\circ C} 2\,RSO_2FeCl_2 + 10\,CO + (RSO_2)_2 \quad (14)$$

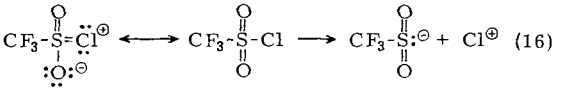
($R = p\text{-}CH_3C_6H_4$)

CF_3SO_2Cl reacts quite differently with binuclear carbonyl complexes:

$$CF_3SO_2Cl + [\pi\text{-}C_5H_5M(CO)_n]_2 \xrightarrow{-20^\circ C} \pi\text{-}C_5H_5M(CO)_nSO_2CF_3 + \pi\text{-}C_5H_5M(CO)_nCl \quad (15)$$

($M = Fe$, $n = 2$[27]; $M = Ni$, $n = 1$[56])

Because of the strongly electron-attracting effect of the trifluoromethanesulfonyl residue on the Cl atom, heterolysis of the CF_3SO_2Cl molecule probably occurs here under the influence of a suitable reagent.



(16)

Perfluoroalkyl iodides behave similarly toward carbonylmetal and π-cyclopentadienylcarbonylmetal complexes[55, 57].

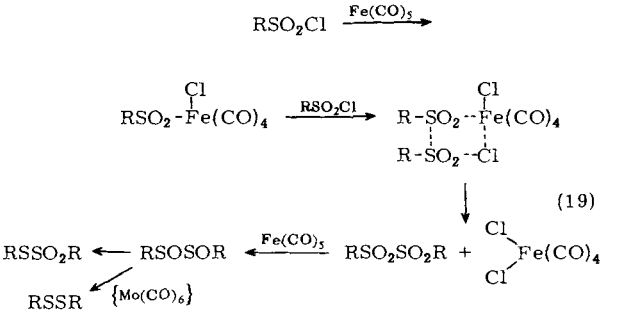
It is interesting to note that the reaction of RSO_2Cl with mononuclear carbonylmetal compounds proceeds further when tetramethylurea (TMU) is used as the solvent. *Alper* found that the reaction with $Fe(CO)_5$ leads to *S*-alkyl (aryl) thiosulfonates[58],

$$RSO_2Cl + Fe(CO)_5 \xrightarrow[TMU]{BF_3\cdot(C_2H_5)_2O} RSSO_2R \quad (17)$$

and the reaction with $Mo(CO)_6$ to disulfides[59].

$$RSO_2Cl + Mo(CO)_6 \xrightarrow[TMU]{} RSSR \quad (18)$$

According to the proposed mechanism[58], this reaction again proceeds *via* $RSO_2Fe(CO)_4Cl$ [cf. also eq. (12)]:



(19)

(c) *Reaction of metal halide compounds with alkaly metal sulfinates:*

$$R'_nMX_m + mRSO_2^- \rightarrow R'_nM(SO_2R)_m + mX^- \quad (20)$$

$$[(n\text{-}C_4H_9)_4N][M(CO_5)I] + RSO_2^- \rightarrow [M(CO)_5SO_2R]^- + [(n\text{-}C_4H_9)_4N]I \quad (21)$$

($M = Cr, W$; $R = C_6H_5$[60])

As has been shown, the preparation methods (a), (b), and (c) are not generally applicable, but supplement one another well.

3.1. Transition Metal Sulfinates

3.1.1. Transition Metals in Low Oxidation States

Of the sulfinatocarbonylmetal compounds of the triads of groups VI, VII, and VIII, only the *S* type is known, for the reasons given in Section 2.2.1.

The electron-attracting CF_3 group causes an increase in the SO_2 stretching frequencies in comparison with unfluorinated derivatives. This naturally requires a correspondingly shorter wavelength for the position of the CO absorptions, which is in fact found in every case. The spectra of the manganese and rhenium complexes are characterized by the occurrence of five absorptions in the region of terminal CO groups. The C_{4v} symmetry is so strongly distorted by the angular RSO_2^- ligands that the B_1 vibration, which is forbidden by the IR selection rules, is also present, and the band due to the E vibration is split.

Table 1. Some characteristic sulfinatocarbonylmetal complexes of the group VI, VII, and VIII triads.

Compound	Preparation (Eq.)	$\nu_{as}(SO_2)$ (cm^{-1})	$\nu_s(SO_2)$ (cm^{-1})	Ref.
$Na[Cr(CO)_5SO_2C_6H_5]\cdot 1.5\,CH_3OH$	(21)	1110 sh 1102 s	1015 s 1001 s	[60]
$Mn(CO)_5SO_2CH_3$	(3, 4)	1201 s 1183 sh	1053 s 1044 sh	[60]
$Re(CO)_5SO_2CH_3$	(3, 4)	1192 s	1054 s	[60]
$\pi\text{-}C_5H_5Mo(CO)_3SO_2CH_3$	(3, 4)	1190 s	1051 s	[61]
$\pi\text{-}C_5H_5Fe(CO)_2SO_2CH_3$	(3, 4)	1194 s 1181 sh	1061 sh 1052 s	[26, 62]
$Mn(CO)_5SO_2C(CH_3)_2CH{=}CH_2$	(3, 4)	1190 s 1176 sh	1041 s	[42, 43]
$Re(CO)_5SO_2C(CH_3)_2CH{=}CH_2$	(3, 4)	1187 s 1173 sh	1045 s	[43]
$Mn(CO)_5SO_2CF_3$	(10)	1220 m	1092 m	[53]
$Re(CO)_5SO_2CF_3$	(10)	1207 m	1091 m	[27]
$Co(CO)_3P(C_6H_5)_3SO_2CF_3$	(10)	1190 s	1097 m	[27]
$\pi\text{-}C_5H_5Fe(CO)_2SO_2CF_3$	(10, 15)	1232 s	1070 m	[27]
$\pi\text{-}C_5H_5Ni(CO)SO_2CF_3$	(15)	1240 sh	1070 m	[56]

3.1.2. Transition Metals in Normal and Higher Oxidation States

Sulfinato complexes of monovalent, bivalent, trivalent, and tetravalent transition metals having the general formulas RSO_2M, RSO_2MR, $(RSO_2)_2M$, $(RSO_2)_3M$, $(RSO_2)_2MR_2$, and $(RSO_2)_4M$ will be described here.

Corresponding to the Ahrland-Chatt classification[38], the RSO_2^- ligand acts as an oxygen donor (sulfinato-*O*) with the 3d metals, whereas mainly sulfinato-*S* derivatives are formed with Pd, Pt, and Hg.

Monosulfinato[19, 63], bis(sulfinato)[3, 5, 28, 31, 51, 56, 64–67], tris(sulfinato)[3, 56, 68], and tetrakis(sulfinato)[68] complexes are obtained by reaction of soluble metal halides or acetates with sodium sulfinates in water, ethanol, or THF at temperatures between 25 and 80 °C in accordance with

$$MX_n + nRSO_2Na \rightarrow nNaX + M(O_2SR)_n \quad (22)$$

(M = 3d, 4d, 5d metal; R = *p*-$CH_3C_6H_4$, C_6H_5, CH_3)

Compounds of the type RSO_2M are known[19] and have been investigated by IR spectroscopy[63] only in the group I triad, with Ag^I (cf. Table 3).

mixed, pure, and perfluorinated arylmercury arenesulfinates $R'SO_2HgR$ (*e.g.* R' = C_6H_5, R = C_6F_5) by reaction of $(R'SO_2)_2Hg$ with HgR_2.

Bonding isomers in which the sulfinato ligand is bonded *via* oxygen in one case and *via* sulfur in the other were isolated for the first time with $C_6H_5SO_2HgC_6H_5$[31, 51, 69]. The *O* type is formed by crystallization from the sulfinato-*S* complex. $C_2H_5SO_2HgC_2H_5$ is of the *S* type in the solid state, whereas the ethanesulfinate group is coordinated *via* oxygen in solution[69].

UV spectra confirm an octahedral configuration of the central ion in the bis(sulfinato)diaquametal(II) complexes (M = Co and Ni, R = C_6H_5; M = Cu, R = C_6H_5, *p*-$CH_3C_6H_4$)[64]. According to the small frequency differences between $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ (cf. Table 3), the RSO_2^- groups are bonded to the metal *via* both oxygen atoms. It cannot be established conclusively from the IR spectrum whether the ligands are linked intramolecularly or intermolecularly to the coordination center M. However, the insolubility of the bis(arenesulfinato)metals in organic solvents and even in water points to a polymeric intermolecular linkage.

Table 2. SO_2 stretching frequencies (in cm^{-1}) of some RSO_2MR complexes.

Compound	$\nu_{as}(SO_2)$ or ν(SO)	$\nu_s(SO_2)$ or ν_{as}(SOM)	Ref.	Bond type
$CH_3SO_2ZnCH_3$	1005 s	955 m 940 m	[2]	Sulfinato-*O,O'*
$C_6H_5SO_2HgC_6H_5$ [a]	1175 vs, b	1048 s	[31, 51,	Sulfinato-*S*
[b]	1048 vs, b	836 vs, b	69]	Sulfinato-*O*
$C_6H_5CH_2SO_2HgCH_2C_6H_5$	1050 s	870 s	[44, 69]	Sulfinato-*O*
$C_6H_5SO_2HgC_6F_5$	1035 m	828 vs	[51]	Sulfinato-*O*

[a] In Nujol; [b] in CH_2Cl_2.

Table 3. SO_2 stretching frequencies (in cm^{-1}) of some RSO_2M and $(RSO_2)_2M$ complexes (solid, KBr; TS = *p*-$CH_3C_6H_4SO_2^-$, BS = $C_6H_5SO_2^-$).

Compound	$\nu_{as}(SO_2)$ or ν(SO)	$\nu_s(SO_2)$ or ν_{as}(SOM)	Ref.	Bond type
BSAg	1027 vs	956 s	[63]	Sulfinato-*O,O'*
$BSAg(OH_2)_n$	1020 vs	970 s	[63]	Sulfinato-*O,O'*
$(TS)_2Cr(OH_2)_2$	970 vs, b	940 vs, b	[56]	Sulfinato-*O,O'*
$(TS)_2Mn(OH_2)_2$	994 s	952 s	[56]	Sulfinato-*O,O'*
$(TS)_2Fe(OH_2)_2$	994 vs	963 s	[56]	Sulfinato-*O,O'*
$(TS)_2Co(OH_2)_2$	983 s	963 m-s 938 vs	[56]	Sulfinato-*O,O'*
$(TS)_2Ni(OH_2)_2$	984 s	945 vs	[56]	Sulfinato-*O,O'*
$(TS)_2Cu(OH_2)_2$	1011	953	[64]	Sulfinato-*O,O'*
$(TS)_2Cu(OH_2)_4$	998	938	[28, 31, 51][a]	Sulfinato-*O*
$(TS)_2Cd(OH_2)_2$	990 vs	965 sh 947 vs	[3, 66]	Sulfinato-*O,O'*
$(TS)_2Cd$	1031 s 1015 s	924 m 904 m	[3]	Sulfinato-*O*
$(TS)_2Hg(OH_2)_2$	1037 vs	980 s	[3]	Sulfinato-*O,O'*
$(TS)_2Hg$	1229 m 1203 vs	1040 vs	[3, 5, 65]	Sulfinato-*S*
$(CH_3SO_2)_2Hg$	1177 vs	1061 vs	[3]	Sulfinato-*S*
$(CF_3SO_2)_2Ni(THF)_2$	1192 vs 1166 vs	1053 s 1040 s 1010 s	[56]	Sulfinato-*O,O'*
$(CF_3SO_2)_2Zn$		1020 s	[70]	

[a] Cf. Section 2.1.

Whereas dialkyl(aryl)zinc[2] and dialkyl(aryl)mercury derivatives[69] take up 1 mole of SO_2 to form RSO_2MR under certain conditions, bis-insertion occurs only with $(CH_3)_2Zn$[1, 2]. *Deacon* and *Felder*[31, 51] have synthesized

The bonding of the RSO_2^- ligands to Zn^{II}, Cd^{II}, and Hg^{II} depends on the water content of the compound[3] (cf. Table 3). The tendency to split off water increases from zinc to mercury. Since Hg^{II}, according to the Chatt-Ahrland clas-

sification[38], is one of the particularly strong b acceptors, it favors the *S*-linkage. Bonding of the RSO_2^- residue to mercury *via* both O atoms is found only in the derivatives containing water, and because of their instability, these immediately split off water to form the *S* type. The b character is considerably weakened in cadmium, while zinc even has strong a-acceptor properties. This explains why the RSO_2^- ligands are always bonded *via* one and two O atoms respectively to these last two metals.

Though the IR spectra of the sulfinatometal chlorides RSO_2MCl [cf. Section 3(b), eq. (12) and (13)] of vanadium[56], chromium[56], molybdenum[56], tungsten[56], iron[27], cobalt[56], and nickel[27,56] provide no definite information about their structures, the position of the symmetric SO_2 stretching vibration in particular indicates that the RSO_2^- group (R = CF_3, *p*-$CH_3C_6H_4$) is bonded to the metal *via* both O atoms ($CF_3SO_2FeCl(THF)_2$: $\nu_{as}(SO_2)$ = 1192 vs, 1156 s, $\nu_s(SO_2)$ = 1001 vs; $CF_3SO_2NiCl(THF)_2$: $\nu_{as}(SO_2)$ = 1192 vs, 1154 s, $\nu_s(SO_2)$ = 975 vs). The asymmetric SO_2 stretching vibrations in CF_3SO_2MCl absorb at surprisingly short wavelengths. This may be caused by coupling of the asymmetric CF_3 and SO_2 stretching vibrations, since the $\nu_{as}(CF_3)$ bands appear at relatively low frequencies. The electronic spectra indicate a pseudooctahedral environment of the central ions for $CF_3SO_2MCl(THF)_2$ (M = Fe, Ni)[27].

The sulfinatometal chlorides RSO_2MCl are formally comparable with the Grignard compounds RMgX in their composition. Their reactivity was therefore investigated, but was found to be much lower; nucleophilic transfer of the RSO_2^- group has never yet been achieved. This seems understandable when one considers that the bidentate character and the associated chelating effect result in considerable strengthening of the metal-ligand bond[56].

The bis(trifluoromethanesulfinato)metal complexes of molybdenum, iron, and nickel are obtained in a rather unusual reaction on treatment of the corresponding bis(π-cyclopentadienylmetalcarbonyls) with CF_3SO_2Cl in a polar medium such as tetrahydrofuran[56]:

$$2\,CF_3SO_2Cl + [\pi\text{-}C_5H_5M(CO)_n]_2 \xrightarrow[THF]{20\,^\circ C} MCl_2 + (CF_3SO_2)_2M + 2\,nCO + 2\,C_5H_5 \qquad (23)$$

(M = Mo, Fe, Ni; n = 3, 2, 1)

The corresponding zinc compound $(CF_3SO_2)_2Zn$ was prepared by reduction of CF_3SO_2Cl with zinc[70]. The $CF_3SO_2^-$ residue appears from the IR spectra (cf. Table 3) to be linked to the metal *via* both oxygen atoms.

Palladium(II) compounds combine with the benzenesulfinate ion to form complexes of the type $(C_6H_5SO_2)_2Pd(OH_2)_2$, $[(C_6H_5SO_2)_2PdX(OH_2)]^-$, and $[(C_6H_5SO_2)_2PdX_2]^{2-}$ (X = Cl, Br), in which the sulfinato ligand is coordinated *via* the sulfur[71] (cf. Table 4). A striking characteristic of these sulfinato complexes is their great formation tendency and the chemical stability of the aqua species. This behavior is also found for sulfito[72] and thiosulfato[73] derivatives, and is evidently characteristic of thio anions bonded *via* S. The thiosulfato and sulfito ligands greatly facilitate substitution *trans* to themselves (*trans* effect)[73,74]; the strong formation tendency of aqua species can be attributed to this effect[75].

Table 4. SO_2 stretching frequencies (in cm^{-1}) of some sulfinato complexes of noble metals (BS = $C_6H_5SO_2^-$, TS = *p*-$CH_3C_6H_4SO_2^-$).

Compound	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$	Ref.	Bond type
$(BS)_2Pd(OH_2)_2$	1195 s 1103 s	1057 s	[71]	Sulfinato-*S*
$Na[(BS)_2PdCl(OH_2)]$	1189 s 1099 s	1051 s	[71]	Sulfinato-*S*
$Li_2[(BS)_2PdCl_2]$	1200 s 1103 s	1060 s	[71]	Sulfinato-*S*
$TSIr(CO)(P(C_6H_5)_3)_2Cl_2$	1240 1220	1065 1055	[76]	Sulfinato-*S*
$TSPt(P(C_6H_5)_3)_2Cl$	1205	1043	[77]	Sulfinato-*S*

The reactivity of the benzenesulfinato derivatives can be best understood by assuming that this ligand also exerts a strong *trans* effect, and the coordinated water is consequently bonded *trans* to a sulfinate group. The *cis* configuration is therefore assigned to $[(C_6H_5SO_2)_2PdX(OH_2)]^-$, $(C_6H_5SO_2)_2Pd(OH_2)_2$, and even $[(C_6H_5SO_2)_2PdX_2]^{2-}$[71].

Phosphane-substituted iridium(I)[76] and platinum(0)[77] complexes add sulfonyl chlorides to form octahedral Ir^{III} and square-planar Pt^{II} derivatives of the *S* type (cf. Table 4).

Tris(sulfinato) complexes are known at present for V, Cr, and Fe[3,68]. In contrast to *p*-$CH_3C_6H_4SO_2MCl_2$ (M = Tl, As; cf. Section 3.2[90,106]), *p*-$CH_3C_6H_4SO_2FeCl_2$ [cf. Section 3(b), eq. (14)] can undergo substitution of both Cl atoms by a sulfinato ligand, again with formation of tris(sulfinato) complexes[56].

Three SO bands with the irreducible representations $A_2 + 2E$ are observed in the IR spectra of all $(RSO_2)_3M$ derivatives (Table 5). This leads to the deduction of an octahedral configuration with D_3 symmetry, which is confirmed by the electronic spectra. The RSO_2^- ligands are linked intramolecularly *via* both O atoms to the central ions. The solubility behavior, all tris(methanesulfinato) complexes being very readily soluble in ethanol, also points to the monomeric structure.

Table 5. SO stretching frequencies (in cm^{-1}) of some tris(sulfinato) and tetrakis(sulfinato) complexes (solid, KBr).

Compound	SO stretching frequencies
$(CH_3SO_2)_3V$	970 sh (A_2), 957 vs (E), 920 vs (E)
$(CH_3SO_2)_3Cr$	964 sh (A_2), 947 vs (E), 925 vs (E)
$(CH_3SO_2)_3Fe$	967 s (A_2), 946 vs (E), 919 vs (E)
$(CH_3SO_2)_4Zr$	997 vs (E), 958 vs (E), 931 vs (B_2)
$(\pi\text{-}C_5H_5)_2Zr(O_2SCH_3)_2$	$\nu_{as}(SO_2) + \nu_s(SO_2)$ 1020 vs, 1009 vs, 972 vs, 943 w

Only mono(sulfinato) compounds of Co^{III} have so far been obtained both by insertion of SO_2 and by oxidation with RSO_2Cl[39-41], *e.g.*

$$[Co(CN)_5R]^{3-} + SO_2 \longrightarrow [Co(CN)_5SO_2R]^{3-}\,[39] \quad (R = CH_2C_6H_5) \qquad (24)$$

$$2\,[Co(CN)_5]^{3-} + RSO_2Cl \longrightarrow [Co(CN)_5SO_2R]^{3-}\,[39] + [Co(CN)_5Cl]^{3-} \qquad (25)$$

(R = CH_3, C_2H_5, C_6H_5, $CH_2C_6H_5$, *p*-$CH_3C_6H_4$, *p*-ClC_6H_4)

In all the Co^{III} sulfinates known at present, the RSO_2^- group is linked to the metal *via* the sulfur, as can be seen from Table 6 (cf. Section 2.2.1).

Table 6. SO_2 stretching frequencies (in cm^{-1}) of some mono(sulfinato-*S*)cobalt^{III} compounds (salen = *N,N'*-ethylenebis(salicylideneiminato), dmgH = dimethylglyoximato).

Compound	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$	Ref.
$[CH_3SO_2Co(CN)_5]^{3-}$	1150	1035	[39]
$[C_6H_5SO_2Co(CN)_5]^{3-}$	1200	1040	[39]
$CH_3SO_2Co(salen)(OH_2)_3$	1197 s, b	1063 s	[40]
$C_6H_5SO_2Co(salen)(OH_2)$	1224 s	1062 s	[40]
$CH_3SO_2Co(dmgH)_2py$	1197	1065	[41]
$C_6H_5SO_2Co(dmgH)_2py$	1234	1058	[41]

Solvent dependence [cf. Section 3(b), eq. (12), (17)] is again found in the preparation of compounds of the types $(RSO_2)_2MR_2$ and $(RSO_2)_4M$:

$$(\pi\text{-}C_5H_5)_2ZrCl_2 + 2CH_3SO_2Na \xrightarrow[THF]{80\,^\circ C} (\pi\text{-}C_5H_5)_2Zr(O_2SCH_3)_2{}^{[68]} + 2NaCl \quad (26)$$

$$(\pi\text{-}C_5H_5)_2ZrCl_2 + 4CH_3SO_2Na \xrightarrow[ethanol]{} (CH_3SO_2)_4Zr + 2NaCl + 2C_5H_5Na{}^{[68]} \quad (27)$$

Both zirconium derivatives exist as sulfinato-*O,O'* complexes (cf. Table 5). In the case of the bis(sulfinato) product, however, intermolecular linkage of the coordination polyhedra *via* RSO_2^- bridges cannot be ruled out on the basis of IR spectroscopy.

The IR spectrum of the diamagnetic $(CH_3SO_2)_4Zr$ contains three strong SO stretching absorptions of the classes $B_2 + 2E$ with small frequency differences. A cubic configuration with D_{2d} symmetry can therefore be assigned to tetrakis(methanesulfinato)zirconium(IV).

3.2. Sulfinates of Main Group Elements

The decomposition of aluminum tris(alkanesulfinate) $(RSO_2)_3Al$ with dilute acids to obtain alkanesulfinic acids, a process that can be used even on the industrial scale, has been known for a long time[78, 79]. All the Al—C bonds are split by SO_2, the first so vigorously that a distinct decrease in the yield of sulfinic acid may be found on introduction of SO_2, corresponding to further reaction of aluminum sulfinate that is already formed with unreacted R_3Al to form $(R_2Al)_2O_2SR_2$[80]. Side reactions are best avoided by the reversed reaction principle[78]. Solvents that complex R_3Al as an ether adduct may also be used[79, 81]. Thus *Baker* and *Sisler*[81] obtained $(C_2H_5SO_2)_3Al$ in the pure state for the first time by this method. SO_2 reacts very poorly with triisobutylaluminum, since apart from steric factors, the latter acts mainly as a reducing agent on SO_2[80]. Alkylaluminum halides react without forming by-products. The conversion of a mixture of $(CH_3)_3Al$ and $AlCl_3$ ("methylaluminum sesquichloride") into methanesulfinic acid[82] is well known.

Sulfonyl chlorides react with alkylaluminum derivatives in a molar ratio of 1:1 to form the alkyl chloride and aluminum sulfinate[83]:

$$RSO_2Cl + R'AlX_2 \longrightarrow RSO_2AlX_2 + R'Cl \quad (28)$$
$$(X = R', Cl)$$

It is assumed that after the electrophilic attack of the aluminum compound on the sulfonyl chloride, the chlorine is cationically removed from the sulfur in a synchronous process, and combines with a negatively charged alkyl group of the organoaluminum compound to form the alkyl chloride.

Alkylation to form the sulfoxide takes place with aromatic sulfonyl chlorides in a molar ratio of 1:2[83]:

$$RSO_2Cl + 2R'AlX_2 \longrightarrow R_2SO + R'Cl + X_2AlOAlX_2 \quad (29)$$
$$(X = R', Cl)$$

This difference in behavior is due to the electron density on the sulfur. The aluminum sulfinate formed in the first reaction step (28) allows the alkylation of the sulfur if the electron density on this atom is reduced to a sufficient degree by an electron-attracting substituent, so that attack by the negatively charged ethyl residue is possible.

In contrast to R_3Al, only one mole of SO_2 is inserted into the C—M bond in trialkylgallium[84], trialkylindium[85], and trialkylthallium[86]. The reason for this difference in the mode of reaction probably lies in the considerably greater affinity of aluminum for oxygen, which causes a striving for the maximum possible coordination number of 6. No SO_2 insertion is observed in halogenated organogallium[87], organoindium[87], or organothallium derivatives[86].

IR spectroscopic studies by *Weidlein*[84, 85, 87, 88] suggest puckered $M_2O_4S_2$ eight-membered ring skeletons (sulfinato-*O,O'*; cf. Section 2.1) for the metal sulfinates of the third main group.

p-$CH_3C_6H_4SO_2Na$ reacts with $TlCl_3$ to form *p*-$CH_3C_6H_4SO_2TlCl_2$, and with Tl^I formate to form *p*-$CH_3C_6H_4SO_2Tl$[90], the structures of which are unknown.

Table 7. SO_2 stretching frequencies (in cm^{-1}) of some metal sulfinates of the third main group.

Compound	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$	Ref.
$[(C_2H_5SO_2)_3Al]_{polym.}$	999 vs	975 vs	[81, 87, 88]
$[(C_2H_5SO_2)_2AlCl]_{polym.}$	1002 vs	950 vs	[87, 88]
$[C_2H_5SO_2AlCl_2]_2$	993 vs	971 s	[87, 88]
$[CH_3SO_2Ga(CH_3)_2]_2$	1017 vs 993 sh	972 vs	[85]
$[C_6H_5SO_2Ga(CH_3)_2]_2$	1005 vs	941 vs	[89]
$[CH_3SO_2In(CH_3)_2]$ [a]	1030 vs 999 vs	951 s	[85]
$[CH_3SO_2Tl(CH_3)_2]$ [a]	1080–965		[86]

[a] Degree of association unknown.

In contrast to the third main group, the reactivity to SO_2 increases from the lighter to the heavier elements in the organo derivatives of the fourth main group. Thus tetraorganosilanes[91] and tetraorganogermanes[91] are not attacked by SO_2, whereas organoplumbanes take up two[92–94] or three[48] moles of SO_2. In the case of tin, the insertion of SO_2 is found to depend on the organo residue. With tetra-*n*-butylstannane and tetraphenylstannane, no reaction products are isolated at a reaction temperature of $-20\,^\circ C$[95]. Since the dissociation energies of the Sn—C bond are roughly equal in tetraethyltin, tetra-*n*-propyltin, and tetra-*n*-butyltin, and are much lower than for $(CH_3)_4Sn$[96], the principal reason in the case of $(n\text{-}C_4H_9)_4S_n$ must be steric factors. The corresponding energy for $(C_6H_5)_4Sn$, on the other hand, is considerably greater[96]; in this case, SO_2 is taken up only at higher temperatures, with formation of $(C_6H_5)_2Sn(O_2SC_6H_5)_2$[97].

Of all the aromatic and saturated aliphatic organotin and organolead halides, only $(C_6H_5)_3SnCl$ and $(C_6H_5)_3PbCl$ react with SO_2, with disproportionation[97].

$$2(C_6H_5)_3MCl + 2SO_2 \xrightarrow[\text{liq. } SO_2]{60^\circ C} (C_6H_5)_2M(O_2SC_6H_5)_2 + (C_6H_5)_2MCl_2 \quad (30)$$

(M = Sn, Pb)

The diphenylmetalbis(benzenesulfinates) of Sn and Pb can also be prepared by direct reaction of the corresponding dihalides $(C_6H_5)_2MCl_2$ with benzenesulfinate and by insertion of SO_2 in $(C_6H_5)_3MO_2SC_6H_5$[97].

Eq. (30) contrasts with the insertion of SO_2 in organoaluminum halides, in which the M—Cl bond remains intact[87].

Since some arenesulfinato complexes of tin are difficult to obtain by SO_2 insertion, the reaction with sodium sulfinates has again proved useful here, particularly for the preparation of tricoordinated, pentacoordinated, and hexacoordinated tin sulfinates[98] [cf. eq. (20)].

$$MX_2 + 2NaO_2SR \xrightarrow[\text{ethanol/}H_2O]{20^\circ C} M(O_2SR)_2 + 2NaX \quad (31)$$

(M = Sn, Pb; X = Cl, NO_3; R = C_6H_5, p-$CH_3C_6H_4$)

The number of bands in the IR spectrum of $Sn(O_2SC_6H_5)_2$ (cf. Table 8) indicates that there is no equivalence in the manner in which the two sulfinato ligands are bonded. The tin atoms are evidently bonded intermolecularly *via* one RSO_2^- residue each (sulfinato-*O,O'*), whereas the second ligand is coordinated to the metal *via* one O atom (sulfinato-*O*). Taking the lone pair of electrons on the tin into account, the latter has a ψ-tetrahedral environment. This proposed structure is supported by Mössbauer spectra[98]. *Donaldson et al.*[99, 100] have suggested the same structure for tin(II) carboxylates. The IR spectrum of $(C_6H_5SO_2)_2Pb$ differs considerably from that of the corresponding tin compound. The structure thus cannot be the same as that proposed for the latter, particularly since the steric effect of the 6s electrons can be disregarded in the case of lead[99]. The small frequency difference between $\nu_{as}(SO_2)$ and $\nu_s(SO_2)$ (Table 8) indicates that *both* RSO_2^- ligands are bonded to the lead *via* oxygen (sulfinato-*O,O'*).

SO_2 acts as an oxidizing agent toward phosphorus(III) compounds[103, 104]. The course of the reaction depends on the particular P^{III} derivative in question. In many cases the reactions proceed in accordance with:

$$2P(XYZ) + SO_2 \longrightarrow 2O{=}P(XYZ) + 1/8\,S_8 \quad (32)$$

$$3P(XYZ) + SO_2 \longrightarrow 2O{=}P(XYZ) + S{=}P(XYZ) \quad (33)$$

In contrast to $TlCl_3$[90], but like $HgCl_2$[105], $AsCl_3$ reacts with camphor-10-sulfinic acid[106] with elimination of SO_2 and HCl and formation of a C—M bond (M = As; cf. also for M = Hg[5, 6, 105]). It is interesting to note that once again only one Cl—M bond is converted into a C—M bond.

Sulfur sulfinates, the so-called bis(benzenesulfonyl) and bis(*p*-toluenesulfonyl) sulfides, disulfides, and trisulfides, have been known for 100 years[107, 108]. However, it was only in 1948 that their structures were elucidated by X-ray studies[109, 110]. The designation "sulfide" is misleading here, since the bivalent sulfur is positively polarized. Thus sulfur disulfinate reacts with nucleophiles as a derivative of S^{2+}[111].

The selenium analogs $Se_n(SO_2R)_2$ are obtained *e.g.* by the following reactions[112–114]:

$$SeOCl_2 + 3NaO_2SR \rightarrow Se(SO_2R)_2 + RSO_3Na + 2NaCl \quad (34)$$

$$Se_2Cl_2 + 2NaO_2SR \rightarrow Se_2(SO_2R)_2 + 2NaCl \quad (35)$$

(R = p-$CH_3C_6H_4$, C_6H_5)

In reactions with nucleophiles, such as sodium ethylxanthate, the sulfonyl group is eliminated as a sulfinate ion. In the diselenium and triselenium derivatives, this takes place without opening of the Se—Se bonds[114].

Foss[114] has suggested unbranched S—Se—Se—S chains for the diselenium disulfinates, which are not, however, isomorphous with the corresponding disulfur disulfinates. The monoselenium disulfinates, on the other hand, have the same structure as the analogous sulfur compounds.

Tellurium disulfinates cannot be prepared by a reaction analogous to eq. (34)[115].

Table 8. SO_2 stretching frequencies (in cm^{-1}) of some sulfinato complexes of tin and lead.

Compound	$\nu_{as}(SO_2)$ or ν(SO)	$\nu_s(SO_2)$ or ν_{as}(SOM)	Ref.	Bond type
$(C_6H_5SO_2)_2Sn$	993 s	917 w	[98]	Sulfinato-*O*
	958 s	897 vs		+ Sulfinato-*O,O'*
$(C_6H_5SO_2)_2Pb$	991 s	932 vs	[98]	Sulfinato-*O,O'*
$[(CH_3)_3SnO_2SCH_3]_4$	993 vs	945 m-s	[91, 95, 101]	Sulfinato-*O,O'*
$(CH_3)_3PbO_2SCH_3$	1001 vs	935 s	[93]	Sulfinato-*O,O'*
	987 vs	916 s		
	970 vs			
$[(CH_3)_3SnO_2SC_6H_5]_n$	994 vs	957 vs	[91, 102]	Sulfinato-*O,O'*
$(CH_2{=}CH)_3SnO_2SCH{=}CH_2$	1001 vs	936 vs	[91]	Sulfinato-*O,O'*
$(C_6H_5)_2Sn(O_2SC_6H_5)_2$	958 s	936 vs	[98]	Sulfinato-*O,O'*
	945 sh			
$(C_6H_5)_2Pb(O_2SC_6H_5)_2$	958	937	[97]	Sulfinato-*O,O'*
$(CH_3)_2Sn(O_2SCH_3)_2$	974 s	941 m	[98]	Sulfinato-*O,O'*
	957 s			
$[\pi$-$C_5H_5Fe(CO)_2]_2Sn(O_2SC_6H_5)_2$	1103	869	[29, 30]	Sulfinato-*O*
	1088	853		

4. Reactivity and Application

4.1. Elimination of SO_2 with Formation of a Carbon-Metal Bond

Since it is characteristic of acyl complexes of transition metals that they undergo decarbonylation to form the corresponding alkyl or aryl derivatives[116], it seemed

interesting to examine the question whether the analogous process, *i.e.* "desulfonylation", is possible with sulfinato complexes. Mass-spectroscopic studies on $RSO_2Mn(CO)_5$ compounds[60, 117] show that the first fragmentation yields $Mn(CO)_5SO_2^+$. The signal for $Mn(CO)_5R^+$ occurs with low intensity, *i.e.* the elimination of SO_2 accounts for only a minor part of the decomposition reactions. π-$C_5H_5Mo(CO)_3SO_2CH_2C_6H_5$[61] was the first transition metal sulfinate that was found both to be formed by insertion of SO_2 and to be degraded by desulfonylation.

Organomercury chlorides are obtained by elimination of SO_2[5, 6, 105]:

$$RSO_2H + HgCl_2 \xrightarrow{>T} RHgCl + SO_2 + HCl \qquad (36)$$

Apart from the formation of camphor-10-arsenic(III) dichloride[106], however, this method has not been used for the synthesis of organometallic derivatives of any other elements. The elimination of SO_2 from $Hg(SO_2R)_2$ in boiling toluene is suitable in many cases for the specific preparation of diarylmercuries[65]. However, this is equivalent to only a partial reaction reversal, since *e.g.* $(C_6H_5)_2Hg$ reacts with liquid SO_2 only to give $C_6H_5HgSO_2C_6H_5$[69]. On the other hand, true reversibility is found for the latter complex, which exists as two bonding isomers (sulfinato-*O* and sulfinato-*S*)[118]. Each isomer gives diphenylmercury in high yield when heated under vacuum, with no change in the bonding of the sulfinato group before the elimination of SO_2. In boiling toluene, the *p*-toluenesulfinato and benzenesulfinato derivatives $RSO_2Ir(CO)(P(C_6H_5)_3)_2Cl_2$[76] are converted into the corresponding *p*-tolyl and phenyl species. However, this type of reaction is not a generally applicable method for the preparation of aryl compounds of the group VIII triad metals, since other arylsulfinates (with R = *p*-ClC_6H_4, *p*-$O_2NC_6H_4$, and *p*-$CH_3OC_6H_4$) do not eliminate SO_2 under the same conditions[76]. Finally, *p*-$CH_3C_6H_4SO_2$-$Pt(P(C_6H_5)_3)_2Cl$ also undergoes desulfonylation, but only at 200 °C[77].

4.2. Ligand Behavior of Sulfinato Complexes

Rearrangement in the bonding of the sulfinato group can be brought about by reaction of sulfinato complexes with suitable ligands. Similar rearrangements have been observed for carbonylmanganese(I) compounds containing thiocyanate[119].

The SO_2 stretching frequencies of substituted sulfinatocarbonylmanganese(I) complexes[120] are considerably lower (cf. Table 9) than those of the unsubstituted complexes[60] (cf. Section 3.1.1). *Hartman* and *Wojcicki*[120] attribute this to further strengthening of the Mn=SO_2R π bond as compared with that in $RSO_2Mn(CO)_5$, together with a decrease in Mn—SO_2R σ character. This may be regarded as resulting from the replacement of the weak base and good π acceptor CO by a strong base and poor π acceptor, *i.e.* amine, phosphane or iodide.

The frequency difference for the SO_2 stretching vibrations in the IR spectrum of $[C_6H_5CH_2SO_2Mn(CO)_3py]_n$[120] is fairly small, and a sulfinato-*O,O'* linkage can therefore be assigned to this compound.

Table 9. SO_2 stretching frequencies (in cm^{-1}) of some substituted sulfinato complexes.

Compound	$\nu_{as}(SO_2)$ or $\nu(SO)$	$\nu_s(SO_2)$ or $\nu_{as}(SOM)$	Ref.	Bond type
$CH_3SO_2Mn(CO)_3bipy$	1148 s	1044 s	[120]	Sulfinato-*S*
$CH_3SO_2Mn(CO)_4P(C_6H_5)_3$	1145 s	1035 s	[120]	Sulfinato-*S*
$[C_6H_5CH_2SO_2Mn(CO)_3py]_n$	1020 s 1013 s	958 s	[120]	Sulfinato-*O,O'*
$[(Fe(bipy)_2Cl_2)_2][CF_3SO_2]_2$	1161 sh 1145 vs 1128 sh	1018 m-s	[32]	ionic
$[p$-$CH_3C_6H_4SO_2Ni(bipy)_2]Cl$	1032 s 1019 s	957 m	[32]	Sulfinato-*O,O'*
$(p$-$CH_3C_6H_4SO_2)_2Mn(en)_2$	1012 vs	977 m	[123]	Sulfinato-*O,O'*
$(p$-$CH_3C_6H_4SO_2)_2Febipy$	1025 sh 1015 vs	972 s-vs	[23]	Sulfinato-*O,O'*
$(p$-$CH_3C_6H_4SO_2)_2Fe(bipy)_2$	1219 vs 1199 vs	1034 m 1012 m	[122]	Sulfinato-*S*
$(p$-$CH_3C_6H_4SO_2)_2Fe(bipy)_2$	1054 vs	918 vs	[122]	Sulfinato-*O*
$(p$-$CH_3C_6H_4SO_2)_2Ni(bipy)_2$	1219 vs 1204 vs	1035 s 1013 s	[122a]	Sulfinato-*S*
$(p$-$CH_3C_6H_4SO_2)_2Ni(bipy)_2$	1055 vs	958 m 943 m-s	[23]	Sulfinato-*O*
$(CF_3SO_2)_2Ni(bipy)_2$	1180 sh 1164 s-vs 1145 vs	985 m-s	[23]	Sulfinato-*O*
$[Fe(bipy)_3][CF_3SO_2]_2$	1158 sh 1146 vs 1125 sh	1019 m-s	[23]	ionic
$[p$-$CH_3C_6H_4SO_2Pt(SnCl_3)(PEt_3)]_2$	1180	941	[33]	Sulfinato-*O,S*
$(C_6H_5SO_2)_2Pt(NH_2C_6H_4CH_3)_2$	1164	1040	[124]	Sulfinato-*S*
$C_6H_5SO_2PdCl(py)_2$	1184	1032	[124]	Sulfinato-*S*

The substitution reactions on $RSO_2Mn(CO)_5$ surprisingly require more drastic conditions than those of $Mn(CO)_5X$ (X = Cl, Br). Examination of the CO frequencies, which are highest for $RSO_2Mn(CO)_5$, should lead one to expect the opposite. Thus factors other than the strength of the Mn=CO π bond must determine the reaction rate for

these complexes if the substitution follows a dissociation mechanism. A similar conflict between the ease with which CO is eliminated and the values of the CO frequencies was discussed earlier by *Angelici* and *Graham*[121].

If compounds of the type RSO_2MCl[27, 56], which attain a coordination number of 6 in solution only by addition of solvent molecules, are exposed to the action of bidentate chelating ligands (L), only the solvent molecules are displaced in the first reaction step:

$$RSO_2MCl \xrightarrow{+L} RSO_2MLCl \xrightarrow{+L} \underset{[ML_3][Cl, RSO_2]}{RSO_2ML_2Cl} \xrightarrow{+L} \quad (37)$$

On further addition of donor ligands, either rearrangement takes place in the bonding of the RSO_2^- group to the metal, or else an RSO_2^- or a Cl^- ion is removed[32].

The structures of the adducts (cf. Table 9) depend essentially on the choice of ligand, the ionic size of the bivalent metal, and the nucleophilic character of the RSO_2^- ligand.

Compounds of the type $(RSO_2)_2M$[56] also add bidentate ligands L:

$$(RSO_2)_2M \xrightarrow{+L} (RSO_2)_2ML \xrightarrow{+L} \underset{[ML_3][RSO_2]_2}{(RSO_2)_2ML_2} \xrightarrow{+L} \quad (38)$$

The addition parameters are the ionic size of the metal[23], the nucleophilic character of the RSO_2^- groups[23], and the solvent[122]. Whereas the reaction of the compound $(p\text{-}CH_3C_6H_4SO_2)_2Fe(OH_2)_2$ with 2,2'-bipyridine (bipy) yields the sulfinato-*O,O'* complex $(p\text{-}CH_3C_6H_4SO_2)_2Fe$bipy in tetrahydrofuran, the same reactants in pyridine give the sulfinato-*S* compound $(p\text{-}CH_3C_6H_4SO_2)_2Fe(bipy)_2$[122] (cf. Table 9). This also shows the influence of the ligand L on the character of the transition metal (cf. Section 2.2.1). By application of the solvent dependency it has also been possible to prepare the *O*- and *S*-bonding isomers of $(p\text{-}CH_3C_6H_4SO_2)_2Fe(bipy)_2$[122] and $(p\text{-}CH_3C_6H_4SO_2)_2Ni(bipy)_2$[122a].

The action of the potentially bidentate ligand ethylenediamine (en) on the sulfinato-*O,O'* complex $(p\text{-}CH_3C_6H_4SO_2)_2Mn(OH_2)_2$ leads to the ionic compound $[p\text{-}CH_3C_6H_4SO_2Mn(en)_2][p\text{-}CH_3C_6H_4SO_2]$, the cation of which can be characterized as $[p\text{-}CH_3C_6H_4SO_2Mn(en)_2][B(C_6H_5)_4]$. On reprecipitation, it changes back into the nonpolar *ionization isomer* $(p\text{-}CH_3C_6H_4SO_2)_2Mn(en)_2$[122, 123].

In the *p*-toluenesulfinato-*S*-platinum(II) complexes[33], such as *cis*- and *trans*-$[p\text{-}CH_3C_6H_4SO_2PtCl(PR_3)_2]$, $[p\text{-}CH_3C_6H_4SO_2PtCl(PR_3)]_2$, and $[(p\text{-}CH_3C_6H_4SO_2)Pt_2Cl_3(PR_3)_2]$, the sulfinato group has a *trans* effect similar to that of tertiary phosphanes. *Chatt* and *Mingos*[33] attribute this to strong electron transfer in the S—Pt σ bond. In complexes of other metals, on the other hand, it has been suggested that the sulfinato group is a weak σ donor and a strong π acceptor[26, 27, 76, 77, 120, 124].

4.3. Possible Applications of Sulfinic Acids and Sulfinates

Sulfinates find diverse applications in industrial processes. Thus in the copolymerization of butadiene and styrene in an emulsion of alkanesulfonic acid with air as the oxidizing agent and higher alkanesulfinic acids as oil-soluble reducing agents, dodecanethiol and iron(III) salts are essential for a favorable reaction course[110]. The optimum pH for fast polymerization varies with the alkanesulfinic acid (C_8 to C_{18} in the series of even, unbranched chains).

The effect of transition metal ions in the redox polymerization of vinyl acetate in solution has been investigated by *Ukita*[111]. Fe^{3+} ions are effective when the concentration of the redox catalyst (*p*-$ClC_6H_4SO_2H$/benzoyl peroxide) is low and the temperature high. Mn and Co ions influence the reaction in a similar manner. Cu^{II} salts also accelerate the polymerization even in low concentrations. The results of the investigations were interpreted as being due to a reaction between the metal ions and the benzoyl peroxide. In a process for the block and solution polymerization of vinyl acetate[113], the induction times are very short if a quaternary catalyst system containing a small quantity of an iron salt as well as an amine, a peroxide, and a sulfinic acid is used. The polymerization process becomes more controllable, and control of the continuous polymerization in particular improves. The addition of the iron salt also improves the ratio of the degrees of polymerization of polyvinyl acetate and of polyvinyl alcohol, *i.e.* the difference between the degree of polymerization of the acetate and that of the polyvinyl alcohol obtained from it by hydrolysis is decreased. This is an advantage in that a less crosslinked polyvinyl acetate whose structure corresponds more closely to that of the final polyvinyl alcohol is obtained.

The activity of catalysts (sulfinic acids combined with an oxygen donor) for the polymerization of monoolefinic systems can frequently be increased by the addition of heavy metal compounds, particularly compounds of metals that occur in several valence states, such as iron or cobalt naphthenate[114], iron(II) acetylacetonate[117], and copper salts[112, 125]. Calcium and strontium salts of aliphatic and aromatic sulfinic acids together with quaternary ammonium derivatives improve polymers of vinyl compounds[115]. Spinnable solutions of acrylonitrile-vinylidene chloride copolymers can be prepared by copolymerization in the presence of a redox catalyst system that contains the morpholinium or diethylammonium salts of *p*-chlorobenzenesulfinic acid[126].

Since solutions of acrylonitrile-vinylidene chloride copolymers containing more than 20% of chlorine readily turn yellow on heating, suitable stabilizers have been sought for a long time. It has been suggested that the sodium, potassium, or zinc salts of α-hydroxy sulfinic acids derived from formaldehydesulfoxylic acid should be used in combination with strong acids. However, the solubility of these salts in the organic solvents, *e.g.* dimethylformamide, is so low that deposition of salt crusts on the spinning nozzles occurs during the continuous spinning process[127]; moreover, they act as stabilizers only at low temperatures. Zinc salts of alkanesulfinic or arenesulfinic acids with no hydroxyl group on the α-carbon atom, on the other hand, have been found to be very suitable[127]; in contrast to the sulfoxylates, these zinc sulfinates are readily soluble in concentrations of more than 1% in dimethylformamide or dimethylacetamide at room temperature.

Silver benzenesulfinate is bactericidal, and prevents the growth of skin fungi without damaging human skin. Even

during the short duration of normal washing, soaps containing arenesulfinato complexes of silver (500 ppm) have a bactericidal effect[19].

Sodium or potassium salts of halogenated arenesulfinic acids change or regulate the growth of plant cells. For example, bean and tomato seeds germinate 5 days earlier and with better results. The falling of ripe apples is delayed by spraying with aqueous sulfinate solutions[128].

Finally, sulfinato complexes of cobalt or nickel may be added to the electrolyte in the electrolytic deposition of metal coatings in order to obtain a highly reflective, compact deposit of cobalt or nickel[18].

5. Outlook and Conclusion

The above discussions show the importance of the sulfinato complexes with regard to their structural diversity and their wide range of industrial applications. Though the catalytic activity of sulfinates has been known for more than twenty years, it is only very recently that interest has been shown in their reaction mechanism and in the elucidation of their structures. It is now possible to prepare sulfinato-*S* and sulfinato-*O* complexes as desired. Further insight into their structure should be provided in the future by X-ray analyses.

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Dehalogenation of α-Haloketones *via* α-Oxocarbonium Ions to Stable Oxonium Salts

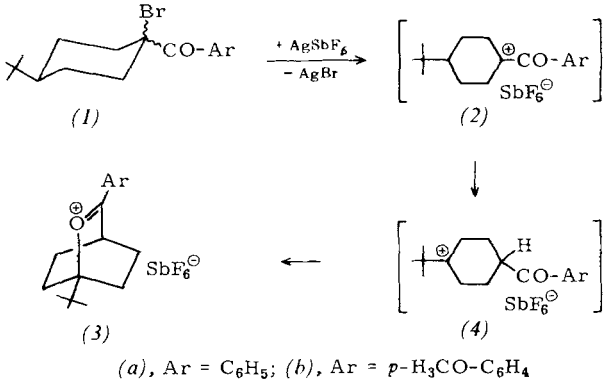
By *Jean Pierre Bégué* and *Micheline Charpentier-Morize*[*]

The existence of α-oxocarbonium ions has only recently been suggested in several reactions[1], including the dehalogenation of α-haloketones[2]. We describe results proving unambiguously the intermediacy of these highly reactive ions.

The two stereoisomeric ketones *(1)* [in the series *a* and *b*] were reacted with the powerful electrophile $AgSbF_6$[3]. Both epimers of *(1)* yielded the same crystalline salt, which is stable at room temperature. Its structure was deduced from its spectroscopic properties and its reactions.

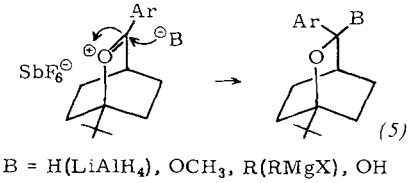
[IR of *(3a)* and *(3b)*: νC=O = 1600 cm^{-1}[4]; NMR ($CDCl_3$), *(3a)*: δ = 7.1—8.5 (5 aromatic H); 4.4 (1 H); 1.8—2.6 (4 CH_2); 1.2 (C_4H_9); *(3b)*: 7.17, 8.37 (4 aromatic H/AB system), J_{AB} = 9 Hz; 4.15 (1 H); 4.04 (OCH_3); 1.75 to 2.5 (4 CH_2); 1.19 (C_4H_9)].

Comparable oxonium ions[5] have similar spectra.



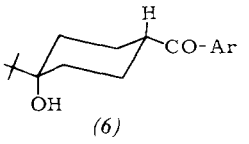
(a), Ar = C_6H_5; *(b)*, Ar = p-H_3CO-C_6H_4

The isolation of 3-aryl-1-*tert*-butyl-2-oxoniabicyclo[2.2.2]-oct-2-ene hexafluoroantimonates *(3a)* implies the initial formation of the α-oxocarbonium compounds 1-benzoyl-*(2a)* and 1-anisoyl-4-*tert*-butylcyclohexylium hexafluoroantimonate *(2b)*, leading by hydride migration (either stepwise or transannular) to the more stable carbonium compounds *(4)* and finally to the salt *(3)*.

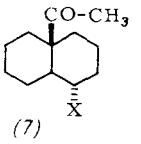


B = H($LiAlH_4$), OCH_3, R(RMgX), OH

(3) reacts with nucleophilic reagents to give the 2-oxabicyclo[2.2.2]octanes *(5)*. Their structure is deduced from IR, NMR, and mass spectra and confirmed by the acid hydrolysis of *(5)*, B = OH, and *(5)*, B = CH_3O, to the ketone *(6)*, which loses water on treatment with iodine in xylene. Compounds similar to *(5)* have been obtained by dehalogenation of the haloketones *(7)*[6]



(6)



(7)

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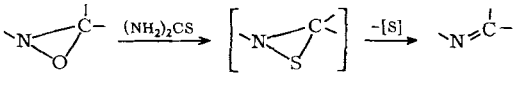
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Deoxygenation of Oxaziranes by Sulfur-Containing Nucleophiles

By *David St. Clair Black* and *Keith G. Watson*[*]

Thiourea, potassium thiocyanate, potassium ethyl xanthate, and potassium selenocyanate are well known to react with oxiranes. In the case of the first three reagents[1–3], thiiranes are formed, but the last reagent[4] converts oxiranes to alkenes, *via* unstable seleniranes, from which selenium is eliminated.

We now report that oxaziranes are deoxygenated, not only by potassium selenocyanate, but also by the above sulfur-containing nucleophiles. The reactions are mild, simple and conversion to the related imine is effectively quantitative. All the above reagents are comparable in their effect, but thiourea is marginally the most convenient.

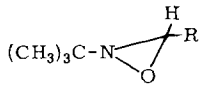


When thiourea and 2-*tert*-butyl-3-phenyloxazirane *(1a)*[5] were heated together under reflux in ethanol for six hours, *N*-benzylidene-*tert*-butylamine[5] was formed in almost quantitative yield and crystalline sulfur was also isolated in 30% yield. These results suggest that the reaction is similar to the conversion of oxiranes to thiiranes and that it proceeds *via* a thiazirane intermediate, from

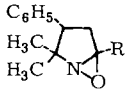
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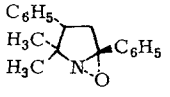
which sulfur is spontaneously eliminated. Thiaziranes have recently been suggested[6,7] as reactive intermediates in the photochemical rearrangement of thiazoles[6] and isothiazoles[7,8], but are as yet unknown.



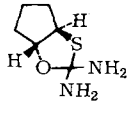
(1a), R = C_6H_5
(1b), R = CH_3



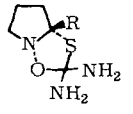
(2a), R = H
(2b), R = C_6H_5
(2c), R = $C(CH_3)_3$



(2d)



(3)



(4)

The reaction of oxaziranes with sulfur-containing nucleophiles is influenced by stereochemical factors to a certain extent. For instance, 2-*tert*-butyl-3-methyloxazirane *(1b)*[9] remained unchanged in the presence of thiourea after twelve hours at room temperature; more vigorous conditions led to extensive tar formation. However, various fused bicyclic oxaziranes were smoothly converted to the related imines. In contrast to *(1b)*, 2,2-dimethyl-3-phenyl-6-oxa-1-azabicyclo[3.1.0]hexane *(2a)*[10] was completely deoxygenated after reaction for eight hours at room temperature. The more hindered oxaziranes *(2b)*[10] and *(2c)*[9] required a reaction temperature of 80 °C for five hours for complete deoxygenation, while compound *(2d)*[10] was only totally converted to the imine after twenty eight hours at 80 °C.

In general, the behavior of fused bicyclic oxaziranes is similar to that of simple ones, in marked contrast to the behavior of some fused oxiranes. Cyclopentene oxide is particularly resistant[2] to any reaction with thiourea or potassium thiocyanate. This result is consistent with the necessary formation of an unfavorable[11] *trans*-fused bicyclic intermediate, *e.g. (3)*, according to the postulated mechanistic pathway[2-3]. However, in the case of bicyclic oxaziranes, a *cis*-fused bicyclic intermediate, *e.g. (4)*, can always be formed, as a consequence of inversion of configuration at the nitrogen atom, even if such inversion is slow[12].

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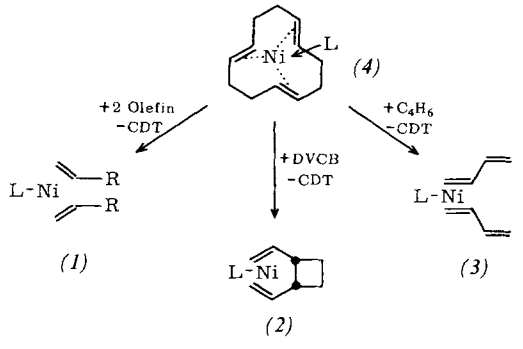
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Bis(olefin)nickel(0) Complexes

By *P. W. Jolly, I. Tkatchenko,* and *Günther Wilke*[*]

The observation[1] that in 1,5,9-cyclododecatrienenickel(0) (CDT·Ni), for example, the *all-trans*-CDT can be exchanged for *all-cis*-CDT led us to attempt to replace the CDT in CDT·Ni·phosphane complexes by other olefins. We report below the preparation and characterization of the new types of bis(olefin)nickel(0) complexes *(1)—(3)*.



L = $P(C_6H_{11})_3$ for *(1a)*, R = H; *(1b)*, R = CH_3; *(1c)*, R = 3-cyclohexenyl; *(2)*; and *(3)*. L = $P(C_6H_5)_3$ for *(1d)*, R = H

Tricyclohexylphosphanebis(ethylene)nickel(0) *(1a)* is formed in 80–90% yield as an almost white precipitate when ethylene is passed into an ethereal suspension of *all-trans*-1,5,9-cyclododecatrienetricyclohexylphosphanenickel *(4)* at −20 °C. *(1a)* reacts with triphenylphosphane at 80 °C with displacement of the theoretical amount of ethylene. The structure of *(1a)* is proved by the IR spectrum [ν(C=C) at 1490 cm^{-1}] and the ^{1}H-NMR spectrum (τ = 7.22/s, $W_{h/2}$ = 4 Hz) (cf. $[(C_6H_{11})_3P]_2NiC_2H_4$, singlet at τ = 7.94[2]).

The complexes *(1b)* and *(1d)* are prepared analogously. The ^{1}H-NMR spectrum of the propene complex *(1b)* [$\tilde{\nu}$(C=C) = 1485 cm^{-1}] shows that several isomers are present in solution. The exchange reaction between propene and $(C_6H_5)_3PNi$—CDT at −20 °C leads only to separation of metallic nickel. The propene in *(1b)* is readily replaced on reaction with ethylene, with formation of *(1a)*.

(1c) and *(2)* are formed on reaction of *(4)* with vinylcyclohexene or divinylcyclobutane (DVCB), respectively, in ether at −20 °C. Both these compounds, which are white powders and extremely sensitive to air, react with CO at −78 °C with quantitative replacement of the vinylcyclohexene or divinylcyclobutane.

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The bis(1,3-butadiene) complex *(3)* is obtained as a yellow, sparingly soluble compound having a somewhat sweet smell on interaction of *(4)* with liquid butadiene for 3 days at −20 °C. Replacement of the butadiene from *(3)* by triphenylphosphane at 80 °C is not quantitative: only 63–65% of the calculated amount of butadiene is found, and vinylcyclohexene, 1,5-cyclooctadiene, and divinylcyclobutane in the ratio 26:6:1 are also formed.

(3) can also be obtained from $[(C_6H_{11})_3P]_2Ni$ and butadiene, a compound $(C_6H_{11})_3PNi \cdot C_4H_6$[4] apparently being formed as intermediate; however, the nitrogen complex, $[[(C_6H_{11})_3P]_2Ni]_2N_2$[3] in toluene affords a product of composition $[[(C_6H_{11})_3P]Ni \cdot C_4H_6]_2 \cdot$ toluene. If *(3)* is treated with *(4)*, a sparingly soluble dimer, probably $[(C_6H_{11})_3P \cdot Ni \cdot C_4H_6]_2$, is precipitated. (For other properties of *(2)* and *(3)* and their relation to the mechanism of dimerization of butadiene on nickel-ligand catalysts see ref.[5].)

Experimental:

Ethylene is passed into a suspension of *(4)*, L = $P(C_6H_{11})_3$ (2.85 g, 5.7 mmole) at −20 °C until the color changes from orange to almost white (4 h). The precipitate *(1a)* is filtered off at −50 °C, washed three times with ether, and dried in a high vacuum (yield 2.0 g, 90%).

cis-Divinylcyclobutane (1 ml) is added dropwise to a suspension of *(4)*, L = $P(C_6H_{11})_3$ (3.55 g, 7.1 mmole) in ether at −20 °C. The mixture is stirred for 3 days at −20 °C and then cooled to −50 °C. The ether is removed and the white product *(2)* is washed three times with ether and dried in a high vacuum (yield 2.85 g, 90%).

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The Mechanism of the Cyclodimerization of Butadiene with Nickel-Ligand Catalysts

By *P. W. Jolly, I. Tkatchenko,* and *Günther Wilke*[*]

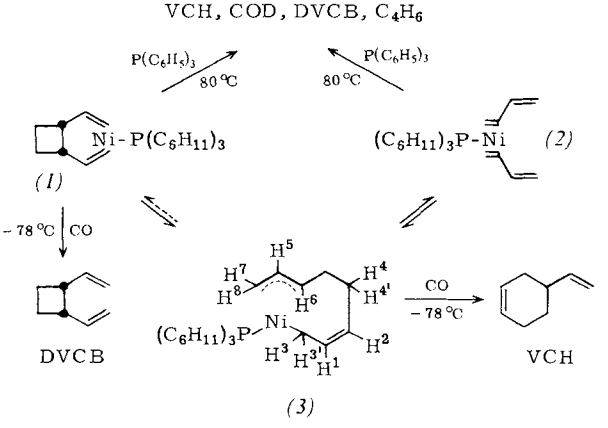
It has been frequently postulated that the transition metal catalyzed cyclooligomerizations of acetylene, 1,3-dienes, and olefins as well as the dismutation of olefins are concerted processes[1]. In particular the dimerization of butadiene to divinylcyclobutane (DVCB) with a nickel-ligand catalyst has been suggested to occur by a concerted mechanism[2]. This formulation, however, is in contrast to the stereochemistry of the isomers obtained from the cyclodimerization of substituted butadienes[3]. For some time now we have held the view that the dimerization is a multi-step process involving, among other intermediates, an α,ω-bisallyl-C_8-chain[4].

The isolation of $(C_6H_{11})_3P \cdot Ni \cdot DVCB$ *(1)* and $(C_6H_{11})_3PNi(C_4H_6)_2$ *(2)*[5] has presented the possibility of investigating this question experimentally and of showing that a multi-step process is involved.

Bis(butadiene)tricyclohexylphosphanenickel(0) *(2)*, a relatively thermally stable yellow compound, reacts with excess triphenylphosphane at 80 °C to give only 65% of the expected butadiene, the remainder being dimerized. In contrast the reaction in solution with CO at −78 °C gives exclusively vinylcyclohexene (VCH).

(1) reacts with CO at −78 °C to produce DVCB. If the same reaction is carried out with a sample which is first left in solution at room temperature for an hour one obtains exclusively VCH. *(2)* may be recovered unchanged from a toluene solution; under the same conditions *(1)* partly rearranges to *(2)*.

From these observations it may be concluded that *(1)* and *(2)* rearrange in solution to a common intermediate. Evidence for this is given by the ^{1}H-NMR spectra of solutions of *(1)* and *(2)* in cyclohexane—identical spectra are obtained which are in agreement with a π-allyl-σ-allyl structure *(3)* [NMR: τ = 4.35 (H^1/2 triplets, $J_{1,2}$ 9 Hz: $J_{1,3} = J_{1,3'}$ 9 Hz); 5.28 (H^2/2 triplets, $J_{1,2}$ 9 Hz; $J_{2,4} = J_{2,4'}$ 7 Hz); 5.88 (H^5/2 triplets, $J_{5,7}$ 8 Hz; $J_{5,6} = J_{5,8}$ 12 Hz) intensity 1:1:1].



Under the influence of an accelerating ligand (*e.g.* CO) ring closure occurs with formation of VCH (cf. the analogous reaction of C_{12}-bis(π-allyl)nickel with CO[6]).

It is also noteworthy that at room temperature in the *solid* state *(1)* rearranges to *(2)*. This shows itself as a color change from white *(1)* to yellow *(2)*, as a decrease in the intensity of the 1482 cm^{-1} band (coordinated C=C) and increase in the intensity of the 1600 cm^{-1} band (free C=C) of *(2)*, as well as in the products obtained by reaction with triphenylphosphane at 80 °C; the volatile hydrocarbon products obtained from freshly prepared *(1a)* and from two months old *(1b)* have different compositions.

(1a): $\sum C_8 = 74\%$, DVCB:VCH:COD = 3.6:1.8:1 as well as 26% C_4H_6
(1b): $\sum C_8 = 62\%$, DVCB:VCH:COD = 4.7:4.3:1 as well as 38% C_4H_6

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This result is in agreement with the observation of *P. Heimbach* and *H. Hey* that butadiene is liberated during the catalytic rearrangement of DVCB to COD and VCH[7].

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[1] a) *G.N. Schrauzer*, Adv. Catalysis *18*, 373 (1968); b) *F.D. Mango*, *ibid. 20*, 291 (1969).

[2] *F.D. Mango*, Tetrahedron Lett. *1969*, 4813.

[3] *P. Heimbach* and *H. Hey*, Angew. Chem. *82*, 550 (1970); Angew. Chem. internat. Edit. *9*, 528 (1970).

[4] *W. Brenner*, *P. Heimbach*, *H. Hey*, *E.W. Müller*, and *G. Wilke*, Liebigs Ann. Chem. *727*, 161 (1969).

[5] *P. W. Jolly*, *I. Tkatchenko*, and *G. Wilke*, Angew. Chem. *83*, 328 (1971); Angew. Chem. internat. Edit. *10*, 328 (1971).

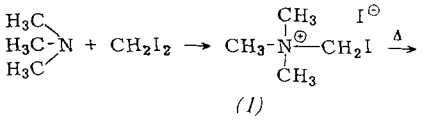
[6] *B. Bogdanović*, *P. Heimbach*, *M. Kröner*, *G. Wilke*, *E.G. Hoffmann*, and *J. Brandt*, Liebigs Ann. Chem. *727*, 143 (1969).

[7] *H. Hey*, Dissertation, Universität Bochum 1969; *P. Heimbach*, Modern Chemistry and Industry, IUPAC-Symposium, Eastbourne 1968, p. 223–31.

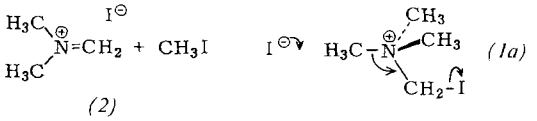
Dimethyl(methylene)ammonium Iodide[1][**]

By *Jakob Schreiber*, *Hans Maag*, *Naoto Hashimoto*, and *Albert Eschenmoser*[*]

We have recently begun to examine a possible parallelism between inversion of pyramidal nitrogen[2] and S_N2 inversion of tetrahedral carbon[3]. This problem, together with that of finding methods for introducing methyl groups into the corrin chromophore[4], has led us to investigate the behavior of (iodomethyl)trimethylammonium iodide *(1)*[5] with nucleophiles. We now describe some preparative results of these studies, namely, a simple and efficient synthesis of dimethyl(methylene)ammonium iodide *(2)*, as well as an example of its use as highly reactive "Mannich reagent"[6].



(1)

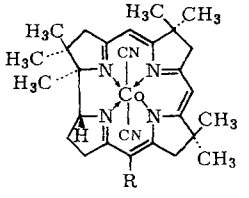


(2) *(1a)*

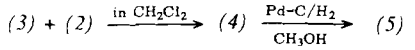
If a solution of the ammonium salt *(1)* (readily obtained from trimethylamine and diiodomethane[5a, 5b]) in tetrahydrothiophene dioxide is heated at *ca.* 150 °C for 10–15 min, methyl iodide distills off and, on cooling, the methyleneammonium salt *(2)* crystallizes from the solution in more than 80% yield. This salt can be recrystallized from the above solvent and sublimed without decomposition at 120 °C/*ca.* 0.05 torr; analytical and spectroscopic data (see below) confirm the structure.

Unlike the iodomethyl derivative *(1)*[7], crystalline tetramethylammonium iodide is thermostable (< 350 °C); moreover, when dissolved in tetrahydrothiophene dioxide, it does not lose methyl iodide at 200 °C to any appreciable extent. We interpret the decomposition *(1)*→*(2)* as an ($n\rightarrow\sigma/\sigma\rightarrow\pi$) fragmentation (possibly occurring concertedly [cf. *(1a)*]) and regard this type of reaction as a variant of the known ($n\rightarrow\pi/\sigma\rightarrow\pi$) fragmentation[8].

The course of the reaction *(1)*→*(2)* suggests the possibility of a new method of demethylating tertiary *N*-methylamines; preliminary experiments indicate that in such a case it is preferable to use more reactive nucleophiles, such as thiophenoxide[9], in the fragmentation step. Use of the salt *(2)* as reagent in reactions of the Mannich type[6, 10] is illustrated by formation of *(4)* from *(3)*.



(3), R = H
(4), R = CH_2-$N(CH_3)_2$
(5), R = CH_3



Stirring a solution of racemic dicyanocobalt(III)-1,2,2,7,7,-12,12-heptamethylcorrin *(3)*[11] in dichloromethane containing an excess of (undissolved) dimethyl(methylene)-ammonium iodide *(2)* for 20 hours at room temperature leads to an 85% yield of the pure, crystalline 15-(dimethylamino)methyl derivative *(4)* in a smooth electrophilic substitution reaction. Assignment of the constitution of this product rests on its characteristic NMR, IR, MS, and UV/visual spectra and is confirmed by hydrogenolytic conversion of *(4)* into the 15-methylcorrin derivative *(5)*, a compound known from earlier work[4]. The reaction sequence *(3)*→*(5)* constitutes a simple method of methylating (sterically unhindered!) meso positions of the corrin system.

Experimental[5a, 5b]:

A mixture of trimethylamine (20 g), diiodomethane (120 g), dioxane (20 ml), and anhydrous ethanol (150 ml) is kept in a closed vessel in the dark for 100 h at room temperature. The crystals formed are filtered off, washed with ethanol and then with ether, and dried for 1 h at 70 °C in a high vacuum. This affords *(1)* (98 g, 89%) as colorless crystals, double m. p.[7] *ca.* 190 °C (dec)/*ca.* 240 °C (dec); the product shows the same melting behavior after recrystallization from ethylene glycol.

A suspension of *(1)* (40.0 g) in tetrahydrothiophene dioxide (120 ml; distilled once from solid KOH and then from CaH_2) is placed in a thoroughly dry four-necked flask fitted with a stirrer and thermometer and tubes for passage of nitrogen, the exit tube leading to a cold trap. The flask is washed out with nitrogen and the reaction mixture is placed in an oil-bath heated to 160 °C whilst it is stirred and a slow stream of N_2 is passed in. The crystals dissolve rapidly at ≈130 °C, methyl iodide is conveyed by the N_2 stream into the cold trap[12], and the decomposition is complete in *ca.* 12 min (temp. ≈150 °C). On cooling in cold water, the salt *(2)* crystallizes directly from the yellow solution; it is filtered off with exclusion of moisture (N_2), washed five times with carbon tetrachloride (50-ml portions), whereupon it becomes almost colorless, and is dried in a high vacuum at 50 °C: this affords *(2)* (18.4 g, 81%),

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as colorless crystals, dec. *ca.* 240 °C, subliming without residue at 120 °C/5 × 10^{-3} torr, and having $\tilde{\nu}(H_2C{=}\overset{\oplus}{N}<)$ = 3115/1682 cm^{-1} (in Nujol)[13], and showing in the NMR spectrum (in dimethyl sulfoxide) two weakly broadened singlets at δ = 8.18 and 3.67 ppm in the intensity ratio 1 : 3[14].

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German version: Angew. Chem. *83*, 355 (1971)

[1] Synthetic Methods, Part 2.—Part 1: *M. Roth, P. Dubs, E. Götschi,* and *A. Eschenmoser,* Helv. Chim. Acta *54*, 710 (1971).

[2] *K. Müller* and *A. Eschenmoser,* Helv. Chim. Acta *52*, 1823 (1969).

[3] *L. Tenud, S. Farooq, J. Seibl,* and *A. Eschenmoser,* Helv. Chim. Acta *53*, 2053 (1970).

[4] *A. Eschenmoser,* Quart. Rev. *24*, 366 (1970); *E. L. Winnacker,* Dissertation, ETH Zürich 1968.

[5] a) *A.-W. Hofmann,* C. R. Acad. Sci. Paris *49*, 880 (1859); b) *E. Schmidt* and *F. M. Litterscheid,* Liebigs Ann. Chem. *337*, 37, 67 (1904); c) *G. Wittig* and *M. H. Wetterling, ibid. 557*, 193 (1947).

[6] To our knowledge, the iodide of the dimethyl(methylene)ammonium ion was previously unknown, although other salts of this ion have been described. For preparation and properties see the extensive studies by *H. Böhme et al.* on (halomethyl)methylamines: *H. Böhme, E. Mundlos,* and *O.-E. Herboth,* Chem. Ber. *90*, 2003 (1957); *H. Böhme* and *K. Hartke, ibid. 93*, 1305 (1960); *96*, 604 (1963); *H. Böhme* and *P. Wagner, ibid. 102*, 2651 (1969); *F. Knoll* and *U. Krumm, ibid. 104*, 31 (1971); also the two following papers: *A. Ahond, A. Cavé, C. Kan-Fan, H. P. Husson, J. de Rostolan,* and *P. Potier,* J. Amer. Chem. Soc. *90*, 5622 (1968); *H. Volz* and *H. H. Kiltz,* Tetrahedron Lett. *1970*, 1917.

[7] (Iodomethyl)trimethylammonium iodide melts with decomposition between 180 and 190 °C, the melt subsequently crystallizing again and then decomposing with blackening above 240 °C. The intermediate solid contains the salt *(2)* (IR spectrum and chemical behavior).

[8] *A. Eschenmoser* and *A. Frey,* Helv. Chim. Acta *35*, 1660 (1952); *C. A. Grob* and *W. Baumann, ibid. 38*, 594 (1955); *C. A. Grob* and *P. Schiess,* Angew. Chem. *79*, 1 (1967); Angew. Chem. internat. Edit. *6*, 1 (1967).

[9] *M. Shamma, N. C. Deno,* and *J. F. Remar,* Tetrahedron Lett. *1966*, 1375.

[10] *H. Hellmann* and *G. Opitz,* Angew. Chem. *68*, 265 (1956); *H. Böhme, E. Mundlos, W. Lehners,* and *O.-E. Herboth,* Chem. Ber. *90*, 2008 (1957).

[11] *J. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnacker,* and *A. Eschenmoser,* Angew. Chem. *79*, 863 (1967); Angew. Chem. internat. Edit. *6*, 864 (1967).

[12] The methyl iodide (b. p. 42 °C; 12.8 g, 73%) trapped at −70 °C was gas-chromatographically homogeneous.

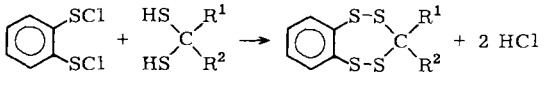
[13] The IR spectra of the product were the same before and after sublimation. C, H, N determinations of the product before and after sublimation gave correct results.

[14] The pentadeuterio-DMSO signal at 2.54 ppm was accompanied by weak signals at 2.7 and 4.5 ppm ($\sum$ *ca.* 0.4 H) due to impurities.

Synthesis of 1,2,4,5-Benzotetrathiepins[1]

By *Franz Fehér, Franz Malcharek,* and *Klaus Glinka*[*]

1,2-Bis(chlorosulfanyl)benzene *(1)*[2] is admirably suited for cyclizing condensation with geminal dithiols *(2)*.



(1) *(2)* *(3)*

Using the dilution principle, we have obtained the 1,2,4,5-benzotetrathiepins *(3a)*, *(3b)*, and *(3c)* by treatment of *(1)* with methanedithiol *(2a)* ($R^1 = R^2 = H$)[3], 1,1-ethanedithiol *(2b)* ($R^1 = H$, $R^2 = CH_3$)[4], and 2,2-propanedithiol *(2c)* ($R^1 = R^2 = CH_3$)[5]. On recrystallization these products are obtained as colorless crystals in good yield. The composition and structures of the hitherto unknown materials *(2b)* and *(3a)–(3c)* were proved by elemental analysis and by mass and NMR spectra. Investigation of the temperature-dependence of the ^{1}H-NMR spectra of *(3a)–(3c)* are in progress.

1,2,4,5-Benzotetrathiepins (3)

100 ml each of solutions were prepared from *(1)* (0.01 mole)[2] in anhydrous carbon tetrachloride and the geminal dithiols *(2)* (0.01 mole) in anhydrous diethyl ether. The pairs of solutions were added dropwise from separate slow-yielding dropping funnels into anhydrous ether (1.8 liters) during 6–8 h, with vigorous stirring and bubbling of a slow stream of dry nitrogen through the reaction mixture. The solvent was removed in a rotatory evaporator, and the residue was treated with warm ethanol. Colorless crystals separated from the filtered ethanolic solution in the cold. *(3a)*, yield 55%, m. p. 92–93 °C, NMR: τ = 6.020 and 5.555 (CH), J = 14.3 Hz[6]. *(3b)*, yield 42%, m. p. 106 °C, NMR: τ = 7.884 and 8.546 (CH_3), 6.120 and 5.495 (CH), J_{CH_3-CH} = 6.7 Hz and 7.5 Hz, respectively. *(3c)*, yield 45%, m. p. 132 °C, NMR: τ = 7.937, 8.470, and 8.274 (CH_3).

Received: February 12, 1971 [Z 370 IE]
German version: Angew. Chem. *83*, 331 (1971)

[1] Chemistry of Sulfur, Part 105.—Part 104: *F. Fehér* and *M. Langer,* Tetrahedron Lett., in press.

[2] *F. Fehér, F. Malcharek,* and *K. Glinka,* Z. Naturforsch. *26b*, 67 (1971).

[3] *T. L. Cairns, G. L. Evans, A. W. Larchar,* and *B. C. McKusick,* J. Amer. Chem. Soc. *74*, 3982 (1952).

[4] Prepared in accord with [3] from acetaldehyde and hydrogen sulfide; yield 15.5%; b. p. 80 °C/85 torr.

[5] *R. Mayer, G. Hiller, M. Nitzschke,* and *J. Jentzsch,* Angew. Chem. *75*, 1011 (1963); Angew. Chem. internat. Edit. *2*, 370 (1963).

[6] KIS 2, Spectrospin A. G., 90 MHz, 24 °C; *(3a)—(3c)* saturated in CS_2.

Higher Amino Acids by Alkylation of α-Metalated Isocyano-acetic or -propionic Esters[1]

By *Ulrich Schöllkopf, Dieter Hoppe,* and *Reinhard Jentsch*[*]

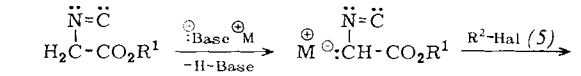
As can be recognized from the numerous studies of the alkylation of *N*-acylmalonic esters[2, 3], considerable preparative importance is attached to the formation of higher amino acids by alkylation of readily accessible, masked, lower α-amino acids[3]. We have now found that simple α-isocyanoalkanoic esters can be alkylated through their derivatives anionized at the α position, to yield higher α-isocyanoalkanoic acids that can be hydrolyzed to amino acids.

Dialkylated isocyanoacetic esters *(9)* (see Table) can be obtained from ethyl isocyanoacetate *(1)* and 2 equivalents of alkylating agent *(5)* in the presence of a base such as potassium *tert*-butoxide or sodium hydride in tetrahydrofuran or ether/DMSO. As a curiosity it may be mentioned that both 1,2-dibromoethane and 2-chloroethyl *p*-toluenesulfonate react with *(1)* undergoing ring closure to ethyl 1-isocyanocyclopropanecarboxylate *(10)*.

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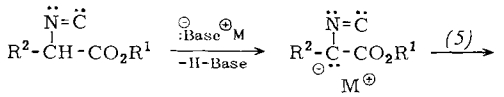
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Essential intermediates are the metalated isocyano esters *(3)* [or *(4)*] and *(8)*. The intermediate alkylation products *(6)* could not as yet be isolated in preparatively satis-



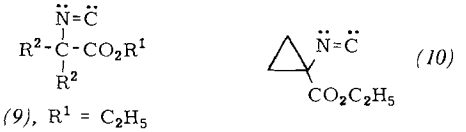
(1), $R^1 = C_2H_5$ *(3)*, $R^1 = C_2H_5$

(2), $R^1 = C(CH_3)_3$ *(4)*, $R^1 = C(CH_3)_3$



(6), $R^1 = C_2H_5$ *(8)*, $R^1 = C_2H_5$

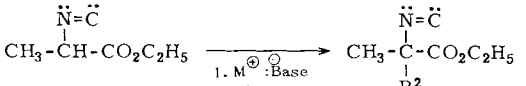
(7), $R^1 = C(CH_3)_3$



(9), $R^1 = C_2H_5$

factory yields because they react further with great rapidity to afford *(8)* and then *(9)*. However, monoalkylated products of type *(7)* can be obtained from *(2)* by way of *(4)*.

Investigations have shown that chain elongation can also be accomplished with ethyl esters of α-substituted isocyanoacetic acid, *e.g.*, with ethyl α-isocyanopropionate *(11)*, from which the ethyl α-isocyano-α-methylalkanoates *(12)* (see Table) can be obtained.



(11) *(12)*

Shaking ethyl 2-isocyanoalkanoates with ether and hydrochloric acid at room temperature converts them into *N*-formylamino esters, which yield amino acids when warmed with aqueous hydrochloric acid or amino ester hydrochlorides when kept in ethanol containing hydrogen chloride; the latter can also be obtained directly from the isocyano compounds. *N*-Formylamino acids are obtained by warming the isocyano ester in ethanolic potassium hydroxide for about 30 min and then acidifying the solution.

General experimental procedures:

Dialkylation of *(1)* with potassium *tert*-butoxide in tetrahydrofuran: A solution of *(1)* (0.02 mole) in THF (10 ml) is added dropwise, with stirring, to potassium *tert*-butoxide (0.04 mole) in anhydrous THF (25 ml) at −60 °C. Then the alkyl halide (0.042 mole) in THF (10 ml) is added at −60 to −50 °C, the cooling bath is removed, and the mixture is allowed to warm to room temperature while stirring is continued. The mixture is stirred until at least 95% of the potassium butoxide used has been consumed (*ca.* 30 min), then the solvent is distilled off at water-pump vacuum (bath-temp. 40 °C), the residue is shaken with ether (50 ml) and water (25 ml), the layers are separated, the aqueous solution is extracted once more with ether, and the combined ethereal solutions are dried over sodium sulfate and distilled.

Dialkylation of *(1)* with sodium hydride in dimethyl sulfoxide/ether: NaH (0.09 mole, suspended in 30 ml of ether) is added dropwise with vigorous stirring to a mixture of *(1)* (0.04 mole) and the alkyl halide (0.084 mole; or 0.042 mole 1,2-dibromoethane) in anhydrous DMSO (40 ml) and anhydrous ether (100 ml) under N_2 at 20–25 °C. When evolution of gas ceases, the mixture is boiled for a further 30 min, poured into ice-water (100 ml), and worked up as above except that ether-extraction is with three 50-ml portions and dissolved DMSO is removed by washing with water (50 ml). For monoalkylation of *(11)* the amounts of alkyl halide, NaH, and solvent are halved.

Monoalkylation of *(2)*: The ester *(2)* (0.04 mole) is dropped, with stirring, into potassium *tert*-butoxide (0.04 mole) in anhydrous THF (50 ml) at not more than −5 °C. This mixture is cooled to −70 °C and then precooled alkyl halide (0.04 mole) is added dropwise. This suspension is added dropwise from a dropping funnel (cooled in methanol-Dry Ice) to THF (50 ml) stirred at 50 °C. The mixture is then heated until a sample dissolved in water reacts only slightly alkaline (*ca.* 30 min), after which it is worked up as above.

Conversion into *N*-formylamino acids: Ethyl α-isocyanoalkanoate (10 mmole) is heated under reflux with KOH (0.6 g) in 90% ethanol (20 ml) for 30 min. The solvent is removed at water-pump vacuum, and the residue is dissolved in water (15 ml), if necessary with gentle warming, and acidified with concentrated hydrochloric acid (1 ml; pH = 1—2). The *N*-formylamino acid, which generally

Table. α-Isocyanoalkanoic esters of types *(7)*, *(9)*, *(10)*, and *(12)* prepared.

Ester	Starting materials and condns. R^2-Hal *(5)*	Condns. [a]	Type	Product R^2	Yield (%)	B.p. (°C/torr)
(1)	n-C_4H_9—I	A	*(9)*	n-C_4H_9	50	84–86/0.6
(1)	n-C_4H_9—Br	B	*(9)*	n-C_4H_9	71	84–86/0.6
(1)	$C_6H_5CH_2$—Br	A	*(9)*	$C_6H_5CH_2$	64	150–153/0.05
(2)	CH_3I	A	*(7)*	CH_3	43	73–75/10
(2)	CH_2=CH—CH_2—Br	A	*(7)*	CH_2=CH—CH_2	76	105–110/10
(2)	$(CH_3)_2$CH—I	A	*(7)*	$(CH_3)_2$CH	35	108–110/12
(2)	$(CH_3)_2$CH—CH_2—I	A	*(7)*	$(CH_3)_2$CH—CH_2	60	55–58/0.1
(2)	$C_6H_5CH_2$—Br	A	*(7)*	$C_6H_5CH_2$	30	110–112/0.1
(1)	Br—CH_2—CH_2—Br	B	*(10)*		58	90–93/15
(1)	Cl—CH_2—CH_2—OTos	B	*(10)*		30	90–93/15
(11)	n-C_4H_9—I	A	*(12)*	n-C_4H_9	59	68–69/1.5
(11)	n-C_6H_{13}—Br	A	*(12)*	n-C_6H_{13}	62	82–85/0.8
(11)	$C_6H_5CH_2$—Br	A	*(12)*	$C_6H_5CH_2$	79	100–105/0.05
(11)	$C_6H_5SCH_2$—Cl	B	*(12)*	$C_6H_5SCH_2$	70	135/0.02

[a] Conditions: A, potassium *tert*-butoxide in THF; B, NaH in ether/DMSO.

separates as an oil, is made to crystallize in an ice-bath, filtered off, and if necessary recrystallized from ethanol or aqueous ethanol.

Conversion into an *N*-formylamino acid ester: Ethyl α-isocyanoalkanoate (20 mmole) is added to 37% hydrochloric acid (0.7 g) in ether (30 ml) at −10°C, and the layers are mixed cautiously (reaction exothermic!) and then shaken for a further 5 min, after which they are neutralized by 1 N-$NaHCO_3$ (12 ml). The organic layer is separated and the aqueous solution extracted again with ether (15 ml). The ethereal solutions are dried over sodium sulfate, and the *N*-formylamino ester is obtained in 80—100% yield by distillation or recrystallization.

Conversion into ethyl 2-aminoalkanoate hydrochloride: An ethyl 2-isocyanoalkanoate (10 mmole) in ethanol (3 ml) is added dropwise at −10°C to a saturated solution (10 ml) of hydrogen chloride in anhydrous ethanol and water (0.25 ml). The mixture is set aside at room temperature for 20 h, then the solvent is removed at water-pump vacuum with exclusion of moisture. This affords a quantitative yield of the amino ester hydrochloride, which crystallizes on cooling and can be purified by recrystallization from anhydrous ethanol, ether, or petroleum ether. Amino ester hydrochlorides are obtained analogously from ethyl *N*-formylamino esters, addition of water and cooling being unnecessary in these cases.

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[1] Syntheses with α-metalated isocyanides, Part 9.—Part 8: *U. Schöllkopf* and *K. Hantke*, Angew. Chem. *82*, 932 (1970); Angew. Chem. internat. Edit. *9*, 896 (1970).

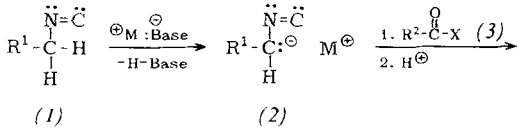
[2] Cf. *A. C. Cope, H. L. Holmes*, and *H. O. House*, Organic Reactions, Vol. IX, p. 107, *1957*.

[3] Cf. *Houben-Weyl-Müller*: Methoden der organischen Chemie. Vol. XI/2. Thieme-Verlag, Stuttgart 1958, pp. 306ff.

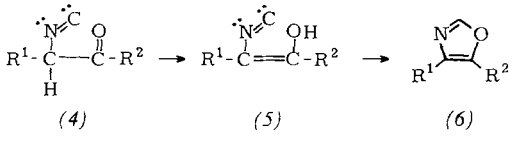
2-Unsubstituted Oxazoles from α-Metalated Isocyanides and Acylating Agents[1]

By *Ulrich Schöllkopf* and *Rolf Schröder*[*]

Oxazoles *(6)* carrying hydrogen on C-2 appear to be difficultly accessible by the usual synthetic methods[2]. We have found that they can be obtained conveniently by treating α-metalated alkyl isocyanides *(2)* [prepared from isocyanides *(1)* and, *e.g.*, potassium *tert*-butoxide or butyllithium] with acylating agents *(3)*. Intermediates in this



(1) *(2)*



(4) *(5)* *(6)*

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Table. Oxazoles *(6)* prepared.

(6)	R^1	R^2	X in *(3)*	B. p. (0°C/torr)	Yield (%)
(a)	$CO_2C_2H_5$	CH_3	Cl	60/0.1	66[a]
(b)	$CO_2C_2H_5$	C_2H_5	Cl	67/0.1	61[a]
(c)	$CO_2C_2H_5$	$CH(CH_3)_2$	Cl	73/0.1	83[a]
(d)	$CO_2C_2H_5$	OC_2H_5	Cl	91/0.1	65[a]
(e)	$CO_2C_2H_5$	$CH_2C_6H_5$	Cl	135/0.1	69[a]
(f)	$CO_2C_2H_5$	C_6H_5	Cl	132/0.1	78[a]
(g)	C_6H_5	H	OCH_3	83/0.2	76[b]
(h)	C_6H_5	$CH(CH_3)_2$	OCH_3	66/0.01	44[b]
(i)	H	$CH_2C_6H_5$	$N(CH_3)_2$	60/0.05	41[b]
(k)	H	$CH(CH_3)_2$	$N(CH_3)_2$	72/70	55[b]
(l)	H	C_2H_5	$N(CH_3)_2$	70/100	48[b]
(m)	H	C_6H_5	$N(CH_3)C_6H_5$	68/0.1	67[b][5]
(n)	$CH{=}C(CH_3)_2$	3,3-dimethyl-oxiranyl	OC_2H_5	56/0.1	50[b][5]

[a] Acyl chloride: isocyanide: base = 1:2:2. 50% of the isocyanide was recovered. Separation by distillation or by hydrolysis of the isocyanide (short shaking with 5 ml of 2 N-hydrochloric acid). $M^{\oplus}$: base$^{\ominus}$ = K *tert*-butoxide.
[b] $M^{\oplus}$: base$^{\ominus}$ = butyllithium.

synthesis are the 2-oxoalkyl isocyanides *(4)* which, *in situ* or during working up, cyclize by way of their enolic forms *(5)*[3].

Ethyl 5-ethoxyoxazole-4-carboxylate (6d)

A solution of ethyl 2-isocyanoacetate[4] (4.52 g, 0.04 mole) is added dropwise, with stirring, to a suspension of potassium *tert*-butoxide (4.5 g, 0.04 mole) in tetrahydrofuran (30 ml) at 0°C. Thereafter a solution of ethyl chloroformate (2.16 g, 0.02 mole) is dropped in, the mixture being kept below 10°C. Solvent is removed at water-pump vacuum (rotatory evaporator), glacial acetic acid (1.2 g, 20 mmole) and water (25 ml) are added, and the mixture is extracted with ether and worked up as usual. Fractional distillation affords ethyl isocyanoacetate (2 g), b.p. 40°C/0.2 torr, and *(6d)* (2.4 g) [NMR(CCl_4): $\tau = 2.4$ (H^2/s); IR (film): ν(C—H) = 3130 cm^{-1}, ν(C≡N) = 1620 cm^{-1}, ν(C=C) = 1510 cm^{-1}].

5-Isopropyloxazole (6k)

A 2.5-N solution of butyllithium (0.04 mol) in pentane is added dropwise over 15 min to a solution of methyl isocyanide[4] (1.64 g, 0.04 mol) in tetrahydrofuran at −70 to −60°C. Then *N*,*N*-dimethylisobutyramide (4.6 g, 0.04 mole) is dropped in at such a rate that the temperature does not rise above −50°C. The mixture is allowed to warm to 0°C, glacial acetic acid (0.04 mol, 2.4 g) is added, the solvent is removed at 25°C in a water-pump vacuum (rotatory evaporator), and the residue is treated with water (25 ml) and extracted with ether. The usual working up affords *(6k)* (2.44 g, 55%) [NMR(CCl_4): $\tau = 2.3$ (H^2/s); IR (film): ν(C—H) = 3130 cm^{-1}, ν(C≡N) = 1580 cm^{-1}, ν(C=C) = 1510 cm^{-1}].

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[1] Syntheses with α-metalated isocyanides, Part 10.—Part 9: *U. Schöllkopf, D. Hoppe*, and *R. Jentsch*, Angew. Chem. *83*, 357 (1971); Angew. Chem. internat. Edit. *10*, 331 (1971).

[2] Cf. *J. W. Cornforth* in *R. C. Elderfield*: Heterocyclic Compounds. Wiley, New York 1957, Vol. 5, pp. 377ff.

[3] For acid-catalyzed cyclization of 2-oxo isocyanides, which are difficult to prepare by conventional methods see *I. Hagedorn*, Angew. Chem. *73*, 26 (1961).

[4] *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer*, and *K. Offermann*, Angew. Chem. *77*, 492 (1965); Angew. Chem. internat. Edit. *4*, 472 (1965).

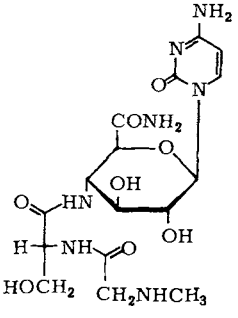
[5] *A. Nürrenbach* and *W. A. Böll*, personal communication.

Synthesis of a Biologically Active Gougerotin Analog[1] [**]

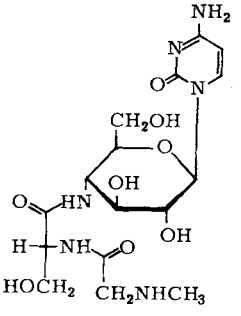
By *Frieder W. Lichtenthaler, Günter Trummlitz, Gerd Bambach,* and *Ivan Rychlík*[*]

In continuation of our investigations aimed at detection of relations between the biological activity of antibiotics of the gougerotin and puromycin type and the structures of the individual components of these aminoacyl aminosugar nucleosides[2, 3], we have now succeeded in synthesizing the first biologically active gougerotin analog, namely a 5'-decarbamoyl-5'-hydroxymethylgougerotin *(2)*[5].

4-Acetamido-1,2,3,6-tetra-*O*-acetyl-4-deoxy-D-glucopyranose *(3)*[6] is converted into the nucleoside tetraacetate *(4)*, m.p. 118—120°C (after sintering around 110°C), $[\alpha]_D^{23} = +46°$ ($c = 1$, CH_3OH), in 36% yield, when treated with 40% HBr/glacial acetic acid for 3 h at 25°C and then with 2,4-diethoxypyrimidine. The constitution *(4)* rests on the NMR spectrum in [D_6]-DMSO (9-Hz doublet at $\tau = 2.10$, acetyl resonances at $\tau = 7.99$, 8.03, 8.14, and 8.20[7]), as well as on IR data (NH at 3310 cm^{-1}), which exclude alternative structures derived from the pyrrolidinose form of the amino sugar.



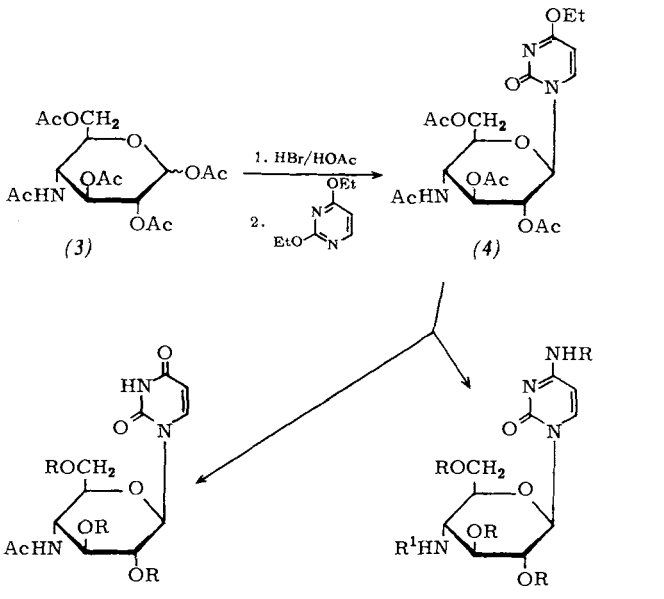
(1)



(2)

Methanolic HCl transforms *(4)*, with hydrolysis of the *O*-ethyl and *O*-acetyl groups, into 1-[4-acetamido-4-deoxy-β-D-glucopyranosyl]uracil *(5)*, a syrup, $[\alpha]_D^{23} = +8°$ ($c = 1$, CH_3OH), and by reaction with methanolic ammonia for 22 h at 95°C 1-[4-acetamido-4-deoxy-β-D-glucopyranosyl]cytosine *(7)*, dec. 290—292°C, $[\alpha]_D^{23} = +34°$ ($c = 1$, H_2O)[8], is obtained in 66% yield. These compounds are unambiguously characterized as the readily crystallizing acetates *(6)*, m.p. 255—260°C (dec.), $[\alpha]_D^{23} = +11°$ ($c = 1$, CH_3OH), and *(8)*, m.p. 294—295°C (dec.), $[\alpha]_D^{25} = +28°$ ($c = 1$, DMF)[8], which are obtained smoothly on acetylation by pyridine and acetic anhydride and afford readily interpretable NMR spectra in both $CDCl_3$ and [D_6]-DMSO.

Removal of the *N*-acetyl group from *(7)* by 4 N HCl in 3 h at 100°C and subsequent deionization lead to the free aminosugar nucleoside *(9)* which, when treated *in situ* with [*N*-(*tert*-butoxycarbonyl)sarcosyl]-D-serine azide[2b] in DMF, affords the dipeptidyl nucleoside *(10)*, dec. 136—138°C, $[\alpha]_D^{23} = +6°$ ($c = 0.4$, H_2O), in 40% yield. Treating *(10)* briefly with trifluoroacetic acid removes the t-BOC protecting group with formation of *(2)*, dec. above 155°C, $[\alpha]_D^{23} = +5°$ ($c = 0.6$, H_2O).



(5), R = H
(6), R = Ac

(7), R = H, R^1 = Ac
(8), R = R^1 = Ac
(9), R = R^1 = H
(10), R = H, R^1 = BOC-Sar-D-Ser

Like *(1)*[9], the gougerotin derivative *(2)*[5] interferes with protein biosynthesis at the peptide-chain elongation stage. In cell-free *E. coli* systems[10] *(2)* interferes with the transfer of the aminoacyl groups from *N*-acetyl-L-phenylalanyl-tRNA, oligosyl-tRNA, or the CACCA-leucine-*N*-acetate

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] Nucleosides, Part 11.—Part 10: [2b].

[2] a) *F. W. Lichtenthaler* and *H. P. Albrecht*, Angew. Chem. *80*, 441 (1968); Angew. Chem. internat. Edit. *7*, 458 (1968); b) *F. W. Lichtenthaler, G. Trummlitz,* and *P. Emig*, Tetrahedron Lett. *1970*, 2061.

[3] This objective, motivated by a biological standpoint, seems to us more relevant than that of total synthesis of gougerotin *(1)* (cf., *e.g.*, [4b]), which, due to existing partial syntheses of the amino sugar [4a], of the nucleoside portion [4b], and now of the dipeptidyl-amino-sugar unit *(2)*, would now have only academic interest.

[4] a) *H. Paulsen, K. Propp,* and *K. Heyns*, Tetrahedron Lett. *1969*, 683; *H. Paulsen, K. Steinert,* and *K. Heyns*, Chem. Ber. *103*, 1599 (1970); b) *K. A. Watanabe, M. P. Kotick,* and *J. J. Fox*, J. Org. Chem. *35*, 231 (1970).

[5] Systematic name for *(2)*: 1-[4-deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine.

[6] Obtained by acetolysis of methyl 2,3,6-tri-*O*-acetyl-4-acetamido-4-deoxy-β-D-glucopyranoside as a syrup, $[\alpha]_D^{23} = +93°$ ($CHCl_3$), which is analytically pure by combustion and, according to the NMR spectrum, contains 85% of the α-form and 15% of the β-form.

[7] For assignment see *F. W. Lichtenthaler, G. Bambach,* and *P. Emig*, Chem. Ber. *102*, 994 (1969).

[8] The data obtained for *(7)* and *(8)* agree with those for the compounds prepared by degradation of gougerotin or by independent synthesis [4b].

[9] Cf. *R. J. Suhadolnik*: Nucleoside Antibiotics. Wiley-Interscience, New York 1970, pp. 172ff.

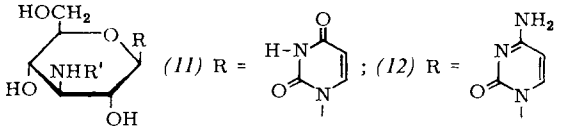
[10] *I. Rychlík, J. Černá, S. Chládek, J. Žemlička,* and *Z. Haladová, J.* Mol. Biol. *43*, 13 (1969); *M. L. Celma, R. E. Monro,* and *D. Vazquez*, FEBS-Lett. *6*, 273 (1970).

[11] *G. Trummlitz*, Dissertation, Technische Hochschule Darmstadt, probably 1971.

[12] *H. A. Friedman, K. A. Watanabe,* and *J. J. Fox*, J. Org. Chem. *32*, 3775 (1967); *H. A. Friedman*, J. Med. Chem. *14*, 174 (1971).

fragment to puromycin. Further, *(2)* inhibits the bonding of CACCA-L-phenylalanine to the acceptor site of the peptidyl transferase, whereas bonding of the *N*-acetyl-leucylpentanucleotide to the donor site is stimulated.

Surprisingly the gougerotin analogs *(11)* and *(12)*[2b] proved inactive in these systems. However, steric considerations may well account for this, as indicated by comparing steric models of *(11)* and *(12)* with those of *(1)* and *(2)* — hydrogen bonds between the OH group on C-2′ and the CO group in the cytosine and between the CO group and the OH group in the serine portion are available for fixing the conformation of the molecules. Whereas the geometrical arrangements of all the important functional groups are the same in *(1)* and *(2)*, completely different steric conditions regarding incorporation at the acceptor site of the 50 S-ribosome apply in the cases of *(11)* and *(12)* owing to 1,3-bonding of the dipeptide portion and the nucleobase[11].



R = Sar-D-Ser

For the same reasons analogs of *(11)* with glycine, sarcosine, L-alanine, phenylalanine, L-lysine, and L-glutamine γ-methyl ester as aminoacyl components (which have been synthesized[12] but apparently not evaluated biologically) are likely to be inactive in these or similar systems.

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Product Ratios on Gas-phase Hydration of Propene

By *Volker Schumacher* and *Kurt Dialer*[*]

Both 1-propanol *(1)* and 2-propanol *(2)* can be produced formally by addition of water to propene; according to Markovnikov's rule the isomer *(2)* is obtained preferentially. We have found that on gas-phase hydration of propene in the presence of various tungsten oxide catalysts the proportion of *(1)* formed is influenced to a surprisingly large extent by the reaction temperature; pressure and residence time are of minor importance in the range studied[1].

The Figure illustrates the observed temperature-dependence of the ratio of *(1)* to *(2)* without consideration of the other reaction parameters; equilibrium values calculated from thermodynamic data[2, 3] are included for comparison. The proportion of *(1)* increases considerably faster with temperature than predicted by thermodynamic equilibrium data. At higher temperatures it exceeds the values calculated from *Rossini*'s data[3]; this indicates a greater reliability of *Green*'s thermodynamic results[2].

Straight lines (probability of error $<1\%$) are obtained by plotting the experimental points in an Arrhenius diagram. This permits the calculation of the differences between the apparent activation energies for hydration of *(1)* or *(2)*; within the range studied (250—370 °C) these values are 23—28 kcal/mole (standard deviation ±6—12%) depending upon the catalyst used. The temperature-dependence

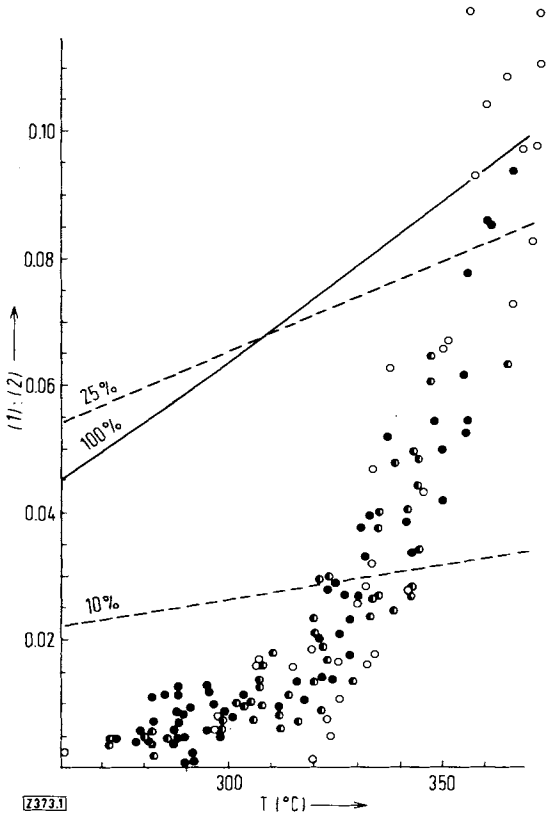


Fig. Temperature-dependence of the ratio of 1-propanol *(1)* to 2-propanol *(2)* formed on hydration of propene (pressure range 40–160 atm; residence time range 2–35 s). Catalysts: ○ 1, ◐ 2, ● 3 (see text). ----: equilibrium values (10% and 25%) according to *Green* [2]; ——: equilibrium values (100%) according to *Rossini* [3].

of the isomer equilibrium as well as the difference in formation enthalpies for the two isomers amount only to a few kcal/mole, and are thus relatively insignificant: the product ratio is primarily determined by kinetic effects.

The greatest proportion of *(1)* was obtained at >350 °C with undoped tungstic acid (catalyst 1), the ratio *(1)*: *(2)* being 0.11. Catalyst 2, in which zinc oxide was used as a promoter as described by *Runge*[4], did not appreciably increase the yield of *(1)* in the range studied. The considerable proportions of by-products, such as dipropyl ether and acetone, were reduced by addition of chromium salts (catalyst 3) without appreciably decreasing the ratio of *(1)* to *(2)*.

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[1] For further details, see *V. Schumacher*, Dissertation, Universität Stuttgart 1970.

[2] *J. H. S. Green*, Trans. Faraday Soc. *59*, 1559 (1963); J. Appl. Chem. *11*, 397 (1961).

[3] *F. D. Rossini*: Selected Values of Physical and Thermodynamic Properties of Hydrocarbons and Related Compounds. A. P. I. Project 44, Carnegie Press, Pittsburgh 1953.

[4] *F. Runge, O. Bankowski*, and *G. Hoffmann*, Brennstoff-Chem. *34*, 330 (1953).

Symmetrical Boc-Amino Acid Anhydrides for Economical Peptide Syntheses on a Solid Phase[1] [**]

By *Theodor Wieland, Christian Birr*, and *Friedlieb Flor*[*]

In peptide syntheses on a solid phase by *Merrifield*'s method[2] the agent used for coupling the Boc-amino acids is now almost exclusively dicyclohexylcarbodiimide (Boc = *tert*-butoxycarbonyl). As maximum yields are essential[3] a three- to five-fold excess of Boc-amino acid and coupling reagent must be used at each step; and recovering the excess of precious amino acid derivative from the reaction mixture requires great effort, if it is at all possible. The mixed anhydride method often used for synthesizing peptides in solution cannot be applied to coupling on a solid phase because the slower reaction in the latter method often leads to a greater or less participation of the wrong acyl group[4]. This induced us to investigate the possibility of using symmetrical anhydrides of Boc-amino acids.

Reverting to experiments by *Wieland* and *Bernhard*[5], we worked out a generally applicable method for preparation of these reactive derivatives; the anhydrides of Boc-Ala, Boc-Phe, Boc-Val, and Boc-Pro were obtained by reaction of the Na salts of the *N*-protected amino acids with phosgene in tetrahydrofuran at −40 to −15 °C. The first three of these compounds were isolated in crystalline form. Boc-Pro anhydride was obtained only as an oil and for our projected syntheses was prepared from the triethylammonium salt in dichloromethane at −15 °C and used *in situ*. The purity of our oily product was proved by its IR spectrum, which showed the characteristic absorption bands around 1825 cm^{-1} (strong) and 1755 cm^{-1} (weak) in the same proportions as in the analytically pure, crystalline anhydrides of the other Boc-amino acids (Table 1).

Table 1. Symmetrical Boc-amino acid anhydrides of type Boc—NH—CHR—CO—O—CO—CHR—NH—Boc.

Anhydride of	M.p. (°C)	IR (cm^{-1})
Boc-Ala	103–10	1830, 1757
Boc-Phe	80–82	1832, 1759
Boc-Val	79–80	1820, 1747
Boc-Pro		1830, 1755

As a sample peptide we have synthesized, on *Merrifield* resin, a linear decapeptide[6], Phe-$(Pro)_2$-$(Phe)_2$-Val-$(Pro)_2$-Ala-Phe, which could be cyclized to well-crystalline antamanide in more than 30% yield[7, 8]. The synthesis was carried out in a "peptide synthesizer" from Schwarz Bioresearch, which had proved its value in our laboratory for the synthesis of several analogous decapeptides by the *Merrifield* technique with dicyclohexylcarbodiimide (DCCI) as coupling reagent[9]. This time our program was modified by replacing the DCCI activation step by addition of three equivalents of the required Boc-amino acid anhydride in solution in CH_2Cl_2. The program included 2 hours' shaking at 20 °C for coupling with the resin-bound peptide, but otherwise the washing program[9] was retained. An advantage of this variant is the absence of dicyclohexylurea, which may be precipitated because of its sparing solubility in many solvents.

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The synthesis was effected starting from carboxyl-terminal Phe on 5 g of resin, 0.385 mmole/g of the acid being bound as ester. After each coupling step, 200 mg of resin was removed for analysis which in each case indicated homogeneity of the synthetic peptide. Fission of 3.7 g of the decapeptide resin by HBr in trifluoroacetic acid gave in all 0.9 g of material (*ca.* 60% yield)[8, 9] that afforded 33.6% of crystalline antamanide identical with the natural product in all respects. In a repetition of the decapeptide synthesis, each Boc-amino acid anhydride was not isolated but was freshly prepared shortly before the coupling and was used in that solution in tetrahydrofuran or CH_2Cl_2, being added in one portion to the reactor[10]; this actually afforded 96% of pure linear decapeptide, which also could be cyclized in 33.5% yield to antamanide with its full biological activity.

The excess of each Boc-amino acid was readily recovered from the respective filtrate in amounts exceeding 80% by hydrolysis of the anhydride with aqueous hydrogen carbonate solution. This permits economic use of any desired excess of the Boc-amino acids and may thus make it possible to realize the objective of 100% yield at each step of a polypeptide synthesis on a solid phase.

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[1] Peptide Syntheses, Part 50. — Part 49: [9].

[2] *R. B. Merrifield*, Advan. Enzymol. *32*, 221 (1969).

[3] *E. Bayer et al.*, J. Amer. Chem. Soc. *92*, 1735 (1970).

[4] Unpublished results from the Dissertation by *F. Flor*, Universität Heidelberg 1971.

[5] *Th. Wieland* and *H. Bernhard*, Liebigs Ann. Chem. *572*, 190 (1951) (experiment by *R. Sehring*).

[6] *Th. Wieland, Chr. Birr*, and *F. Flor*, Liebigs Ann. Chem. *727*, 130 (1969).

[7] *Th. Wieland, J. Faesel*, and *W. Konz*, Liebigs Ann. Chem. *722*, 197 (1969).

[8] *W. König* and *R. Geiger*, Liebigs Ann. Chem. *727*, 125 (1969).

[9] *Th. Wieland, Chr. Birr*, and *A. v. Dungen*, Liebigs Ann. Chem., in press.

[10] NaCl formed from the Na salts of the Boc-amino acids and phosgene blocks the frit and must therefore be removed by washing with THF/water (1:1) and three times with THF.

Stereospecific Synthesis of Optically Pure Quinic Acid and Shikimic Acid from D-Arabinose

By *Hans Jürgen Bestmann* and *Hans August Heid*[*]

In Memoriam Rudolf Grewe

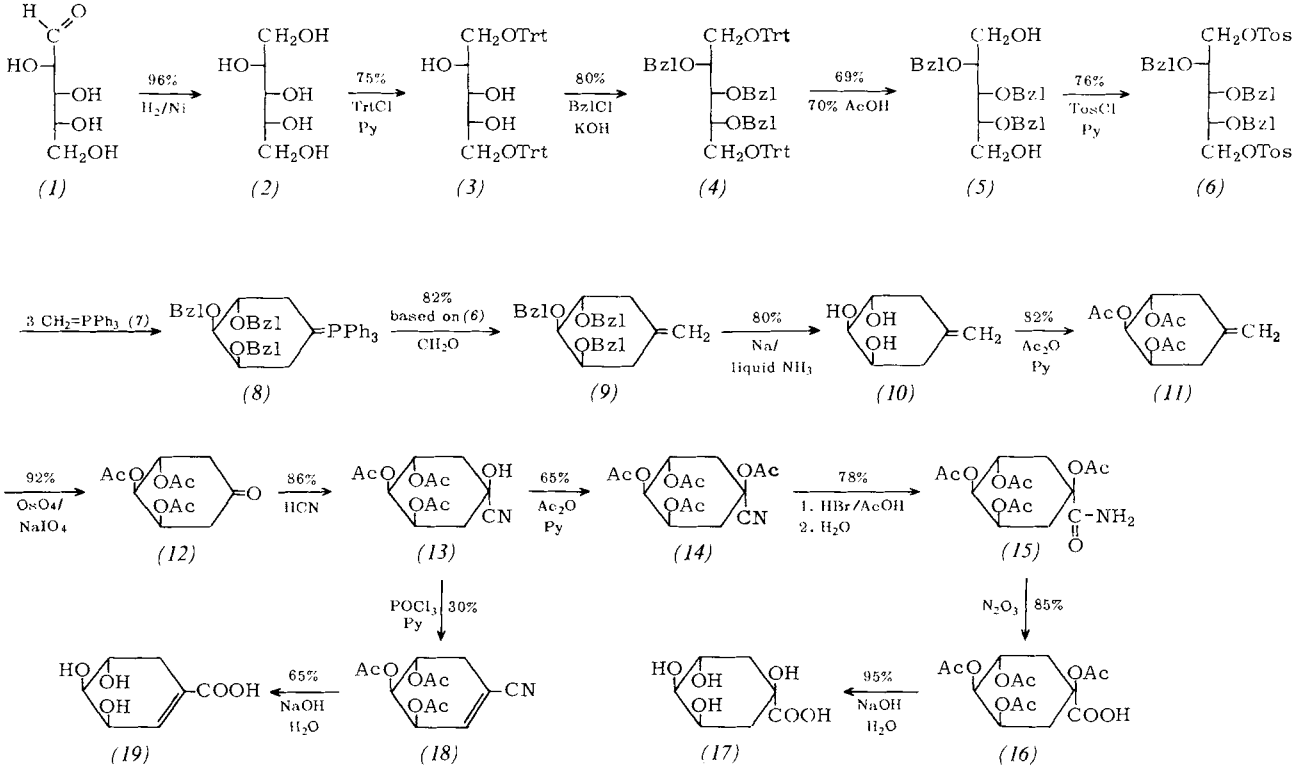
Total syntheses of racemic quinic acid[1] and shikimic acid[2] have been reported, but hitherto no success has attended the many attempts, by numerous schools, to prepare optically pure quinic acid *(17)* and shikimic acid *(19)* from a sugar. We describe below such a synthesis (Scheme 1).

D-Arabinose *(1)* was reduced catalytically[3] by Raney nickel to the arabitol *(2)*, and this was converted[4] by triphenylmethyl chloride into the 1,5-ditrityl derivative *(3)*, which was benzylated, to give *(4)* by anhydrous KOH

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and benzyl chloride. 70% acetic acid detritylated *(4)* to 2,3,4-tri-*O*-benzyl-D-arabitol *(5)*, which was then ditosylated[5] by *p*-toluenesulfonyl chloride in pyridine, affording *(6)*.

The cyclic ylide *(8)* was obtained from *(6)* by a method described previously by us[6] involving methylenetriphenylphosphorane *(7)* (molar ratio 1:3); in this process the third equivalent of *(7)* is required for formation of *(8)* from the corresponding phosphonium *p*-toluenesulfonate first produced[7]. A Wittig reaction of *(8)* with formaldehyde leads to the methylene compound *(9)* (boils in a rotating bulb-tube at a bath-temperature of 180—186 °C and 0.05 torr; $[\alpha]_D^{20} = -36.4°$, $c = 7.3$ in CCl_4), which is debenzylated by sodium in liquid ammonia to crystalline (1*R*,2*S*,3*R*)-5-methylene-1,2,3-cyclohexanetriol *(10)*, m. p. 147 °C, $[\alpha]_D^{20} = -19.5°$ ($c = 6.6$ in water after 48 h). Acetylation of *(10)* by acetic anhydride affords the oily triacetate *(11)*, b. p. 120 °C/0.2 torr, $[\alpha]_D^{20} = -63.8°$ ($c = 3.5$ in CCl_4), oxidation of which by $NaIO_4/OsO_4$[8] affords the ketone *(12)* which was prepared by *Grewe*[9] from naturally occurring quinic acid.



Scheme 1. Abbreviations: Ac = acetyl; Trt = trityl; Py = pyridine; Bzl = benzyl; Tos = tosyl; Ph = phenyl.

Further steps in our synthesis are based on the fundamental work of *Grewe*. *(12)* is converted in a cyanohydrin synthesis stereoselectively into the triacetylquinic acid nitrile *(13)*, which is acetylated[9] to the tetraacetyl derivative *(14)* and agrees in all its physical and spectroscopic properties with a comparison specimen prepared by *H. O. L. Fischer*'s method[10]. HBr in glacial acetic acid hydrolyzes the nitrile *(14)* to the amide *(15)*, whence liquid N_2O_3 provides the known tetraacetylquinic acid *(16)*. Hydrolysis of *(16)* by aqueous sodium hydroxide solution and subsequent treatment with an ion-exchanger affords the free quinic acid *(17)*, m. p. 161 °C, $[\alpha]_D = -43.8°$ ($c = 6$ in water), that is identical with the natural product.

The following route leads to shikimic acid: The cyanohydrin *(13)* is dehydrated by *Grewe*'s method[9] with $POCl_3$ in pyridine stereospecifically to triacetylshikimonitrile *(18)*. After hydrolysis thereof, we were able to isolate free shikimic acid *(19)* with m. p. 189 °C and $[\alpha]_D = -179.7°$ ($c = 4$ in water), which also was identical with the natural product.

Compounds *(15)*, *(16)*, and *(18)* agree in all their spectral and physical properties with authentic materials obtained from the natural materials *(17)* and *(19)*[9-11].

The synthesis described above can also be used for preparation of optically pure quinic and shikimic acid labeled with ^{14}C or tritium at various positions.

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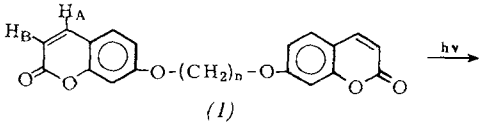
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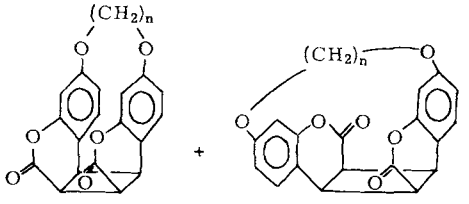
Intramolecular Photocycloaddition of 7,7'-Polymethylenedioxycoumarin[**]

By *Luc Leenders* and *Frans C. De Schryver*[*]

We recently reported the intramolecular photocycloaddition of *N,N'*-alkylenedimaleimides[1] and now wish to describe the analogous reaction of polymethylenedioxycoumarins *(1)*.



(1)



(2) *(3)*

The cyclomers formed must have an *endo*-configuration in view of the shortness of the polymethylene linkage. However, two regioisomers *(2)* and *(3)* are possible and their respective configurations have been elucidated by determination of the dipole moments[6]. The dipole moments for cyclomers *(2a)* and *(3a)*, measured in dioxane, are 6.7 and 2.0 D. The cyclomer with the greatest dipole moment can only be the isomer with a head-to-head structure *(2a)*. This is in agreement with the different solubilities of the two photoproducts in solvents with different polarities.

The configurations of the cyclomers derived from *(1b)* and *(1c)* are determined by comparison of their NMR spectra with those of *(2a)* and *(3a)* respectively. – The presence of oxygen did not inhibit the reaction.

Procedure:

In a typical photolysis, 1.092 g of 7,7'-trimethylenedioxycoumarin *(1a)* was dissolved in 300 ml dichloromethane (concentration 10^{-2} mole l^{-1}), degassed, sealed off, and irradiated in a Rayonet UV Reactor at 350 nm for 72 hours. The solvent was evaporated off on a rotary evaporator.

(1)							*(2)* + *(3)*				
			IR (ν, cm^{-1}) [b]		NMR (δ) [c]					IR (ν, cm^{-1}) [b]	
[a]	*n*	M. p. (°C)	C=O	C=C *cis*	H_A	H_B	[a]	Yield (%)	M. p. (°C) [d]	C=O	NMR (δ) [e]
(1a)	3	184–185.5	1720	3050, 1400	7.88	6.22	*(2a)*	37	241	1760	4.33
							(3a)	60	271	1752	4.08
(1b)	4	182–183.5	1717, 1708	3045, 1400, 1390	7.83	6.17	*(2b)*	42	252	1765	4.30
							(3b)	56	279	1750	4.08
(1c)	5	138–138.5	1725, 1709	3060, 1408, 1395	7.90	6.21	*(2c)*	45	236.5	1760	4.25
							(3c)	52	291.5	1748	4.09

[a] All compounds gave correct elemental analysis data and mass spectra.
[b] In KBr.
[c] Resonance signals of the vinyl protons; these signals are doublets. All spectra were recorded in [D_6]-DMSO.
[d] All compounds sublime.
[e] Resonance signals of the four cyclobutane protons. All spectra were recorded in [D_6]-DMSO.

Direct and sensitized photodimerizations of coumarin have been reported in the literature[2]. Irradiation in solution gives a mixture of three isomers: the *endo* head-to-head dimer; the *exo* head-to-head dimer; and the *endo* head-to-tail dimer[3]. Photodimers of several substituted coumarins have also been prepared, *e.g.* 7-methoxycoumarin has been photodimerized in the solid state[4].

7,7'-Polymethylenedioxycoumarins *(1)* have been prepared in analogy with the synthesis of 7,7'-methylenedioxycoumarin[5]. The physical data of the compounds studied are reported in the Table.

The photoreactions are carried out in dichloromethane. The absorption characteristics of the —CH=CH— system in the IR and NMR spectra disappeared upon irradiation, only to be replaced by peaks that can be attributed to a cyclobutane system.

The intramolecular nature of the cycloadducts was proved by mass spectrometry.

The IR spectrum indicated that reaction was complete. The residue was taken up in dry benzene. 0.255 g (23%) isomer *(2a)* precipitated on cooling. The NMR spectrum of the residual reaction mixture shows the presence of additional 14% of isomer *(2a)*. Isomer *(3a)* was separated and purified by column chromatography on Florisil (60–100 mesh) with chloroform as eluent. The isomers were recrystallized from toluene.

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A Reagent for Direct Nucleophilic Carbamoylation[**]

By *Peter Jutzi* and *Friedrich-Wilhelm Schröder*[*]

One-stage nucleophilic transfer of carbonyl groups is of practical interest in preparative chemistry, but only few examples of this type of reaction have been recorded previously[1-4]. In our studies of the reaction of carbon monoxide with element-lithium bonds[4,5] we have obtained a nucleophilic carbamoylating agent that is stable under normal conditions.

If carbon monoxide is led into a solution of lithium *tert*-butylamide *(1)*[6] in benzene/ether at about 50 °C carbon monoxide is inserted into the nitrogen-lithium bond and orange-yellow *tert*-(butylcarbamoyl)lithium *(2)* is obtained:

$$(CH_3)_3C{-}NHLi + CO \rightarrow$$
(1)

$$(CH_3)_3C{-}NH\underset{\underset{O}{\|}}{C}{-}Li \rightleftharpoons (CH_3)_3C{-}NH{-}\ddot{C}{-}OLi$$
(2)

The existence of *(2)* is proved by reaction with trimethylsilicon, -germanium, or -tin chloride, in which lithium chloride is split off and the new types of carbamoyl-substituted Si, Ge, and Sn derivatives *(3)*, *(4)*, and *(5)* are formed in yields of up to 55%:

$$(2) + (CH_3)_3ElCl \xrightarrow{-LiCl} (CH_3)_3C{-}NH{-}\underset{\underset{O}{\|}}{C}{-}El(CH_3)_3$$

El = Si, Ge, or Sn *(3), (4), (5)*

Cpd.	El	B.p. (°C/torr)	IR, $\tilde{\nu}$(C=O) (cm^{-1})	^{1}H-NMR [a] δ-C(CH_3)$_3$	δ-El(CH_3)$_3$
(3)	Si	143/760	1643	−66	−13
(4)	Ge	97/55	1634	−73	−30
(5)	Sn	46/0.01	1625	−79	−29 [b]

[a] ^{1}H-NMR spectra: *ca.* 20% solutions in CCl_4; shifts in Hz from TMS to lower field strengths.
[b] $J(^{119}Sn{-}C{-}H) = 60$ Hz; $J(^{117}Sn{-}C{-}H) = 58$ Hz.

Formation of an $>N{-}\underset{\underset{O}{\|}}{C}{-}Li$ group has so far been demonstrated only when stabilized by complex formation in its isomeric carbene form and if further reactions were carried out at −70 °C[2].

Steric reasons seem responsible for the surprising stability of the uncomplexed compound *(2)*. Thus a suspension of lithium dimethylamide in hexane also reacts with carbon monoxide, absorbing an equimolar amount of this gas in an exothermal reaction, but it was not possible to isolate a dimethylcarbamoyl derivative; treatment with chlorotrimethylsilane gave only oligomeric products and hexamethyldisiloxane.

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π-Allylcarbonylmetals from σ-Allylorganotin Compounds

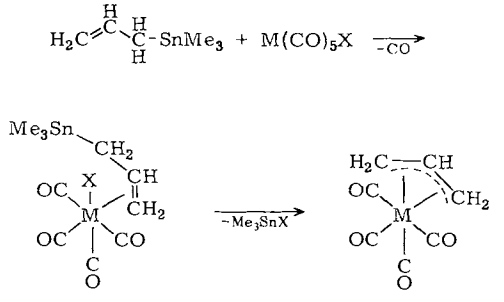
By *E. W. Abel* and *S. Moorhouse*[*]

σ-Cyclopentadienyltrimethyltin has been shown[1,2] to form π-cyclopentadienyl derivatives of carbonylmetals. Continuing to study the utility of organotin derivatives as synthetic intermediates[3,4], we have investigated the transfer of the allyl group from σ-allyltrimethyltin to transition metals. We now report on the advantages of the method for the preparation of π-allyl derivatives of transition metals and, in particular, on the synthesis of some π-allylcarbonylmetals.

π-Allyltetracarbonylmanganese has been prepared[5] by the thermal decarbonylation of σ-allylpentacarbonylmanganese (80 °C/12 h). Such decarbonylations are not always facile, and to date π-allyltetracarbonylrhenium has not been prepared by this route[6].

In contrast, allyltrimethyltin and the pentacarbonyl halides of both manganese and rhenium react to form directly the π-allyltetracarbonylmetal in good yield under mild conditions. As noted above the decarbonylation of σ-allylmanganese pentacarbonyl requires moderately forcing conditions[5]. Thus it would appear that no σ-metal complexes are formed as intermediates in our reactions; and careful monitoring of the reaction by infrared spectroscopy at all stages has failed to indicate the presence of intermediate σ-complexes.

We propose, therefore, that as in many other ligand transferences involving organotin intermediates[3,4] the initial step is one of ligand coordination. This places the organotin group in position for an intramolecular elimination of organotin halide which converts the coordinated olefin to a π-allyl ligand (Scheme 1).



Scheme 1. M = manganese or rhenium, X = chlorine or bromine.

Similar high yield reactions occur with the dimeric $[Mn(CO)_4Br]_2$ and the anion $Mn(CO)_4Br_2^-$. In the former,

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the initial step presumably involves halogen bridge fission[7] to give the olefin-coordinated intermediate, without loss of carbon monoxide, and in the latter displacement of halide ion[8] by the olefin will give the same intermediate.

In the case of many substituted-allyl organotins, the method of their synthesis gives a mixture of two isomers, but for their use in these reactions this is unimportant since the final step of organotin halide elimination gives an identical product from the two isomers. In this light the isomeric mixtures are utilized unseparated.

We have found the shelf-life of allyl-organotins to be infinite, and therefore they are excellent as easily accessible sources for the synthesis of π-allyls. The Table shows a range of allyl- and substituted-allylcarbonylmetals synthesized by this method. In addition we have found the organotin cyclopentadienyls, indenyls, and fluorenyls to be very convenient intermediates for the formation of the respective carbonylmetals having π-bonded ligands.

Table. π-Allylcarbonylmetal complexes from carbonylmetal halides and organotin compounds [a] (Me = methyl).

Reactants	Product	Yield (%)
$CH_2{=}CH{-}CH_2SnMe_3 + Mn(CO)_5Br$	$(\pi\text{-}CH_2CHCH_2)Mn(CO)_4$	82
$CH_2{=}CH{-}CH_2SnMe_3 + Re(CO)_5Cl$	$(\pi\text{-}CH_2CHCH_2)Re(CO)_4$	80
$CH_3CH{=}CH{-}CH_2SnMe_3$ / $CH_2{=}CH{-}CH(CH_3)SnMe_3$ + $Mn(CO)_5Br$	$(\pi\text{-}CH_3CHCHCH_2)Mn(CO)_4$	70
$CH_3CH{=}CH{-}CH_2SnMe_3$ / $CH_2{=}CH{-}CH(CH_3)SnMe_3$ + $Re(CO)_5Br$	$(\pi\text{-}CH_3CHCHCH_2)Re(CO)_4$	60
$CH_2{=}C(CH_3)CH_2SnMe_3 + Mn(CO)_5Br$	$[\pi\text{-}CH_2C(CH_3)CH_2]Mn(CO)_4$	65
$CH_2{=}C(CH_3)CH_2SnMe_3 + Re(CO)_5Cl$	$[\pi\text{-}CH_2C(CH_3)CH_2]Re(CO)_4$	60
$C_6H_5CH{=}CH{-}CH_2SnMe$ / $CH_2{=}CH{-}CH(C_6H_5)SnMe_3$ + $Mn(CO)_5Br$	$(\pi\text{-}C_6H_5CHCHCH_2)Mn(CO)_4$	82
$C_6H_5CH{=}CH{-}CH_2SnMe_3$ / $CH_2{=}CH{-}CH(C_6H_5)SnMe_3$ + $Re(CO)_5Br$	$(\pi\text{-}C_6H_5CHCHCH_2)Re(CO)_4$	65
$CH_2{=}CHCH_2SnMe_3 + [Ru(CO)_3Cl_2]_2$	$(\pi\text{-}CH_2CHCH_2)_2Ru(CO)_2$	10
$CH_2{=}CHCH_2SnMe_3 + [Rh(CO)_2Cl]_2$	$(\pi\text{-}CH_2CHCH_2)Rh(CO)_2$	30
$C_5H_5SnMe_3 + Mn(CO)_5Br$	$\pi\text{-}C_5H_5Mn(CO)_3$	82
$C_5H_5SnMe_3 + Re(CO)_5Br$	$\pi\text{-}C_5H_5Re(CO)_3$	88
$C_5H_5SnMe_3 + [Rh(CO)_2Cl]_2$	$\pi\text{-}C_5H_5Rh(CO)_2$	85
$CH_3C_5H_4SnMe_3 + Mn(CO)_5Br$	$\pi\text{-}CH_3C_5H_4Mn(CO)_3$	59
$CH_3C_5H_4SnMe_3 + Re(CO)_5Cl$	$\pi\text{-}CH_3C_5H_4Re(CO)_3$	40
$indenylSnMe_3 + Mn(CO)_5Br$	$\pi\text{-}C_9H_7Mn(CO)_3$	62
$indenylSnMe_3 + Re(CO)_5Br$	$\pi\text{-}C_9H_7Re(CO)_3$	78
$indenylSnMe_3 + [Rh(CO)_2Cl]_2$	$\pi\text{-}C_9H_7Rh(CO)_2$	70
$fluorenylSnMe_3 + Mn(CO)_5Br$	$\pi\text{-}C_{13}H_9Mn(CO)_3$	20

[a] All products were characterized by satisfactory elemental analysis, infrared, NMR, and mass spectroscopy.

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A Kinetic Procedure for Detection of Short-lived Photointermediates[**]

By *Gerd Kaupp*[*]

A kinetic model was recently developed[1, 2] that in suitable cases permits differentiation of concerted from two-step singlet photoreactions without reliance on energetic data[3]. We now report the application of this model to the elucidation of the mechanism involved in the synthesis of compounds containing the quadricyclane skeleton *(3)*. Quantum yields, qualitative fluorescence studies, solvent and substitution effects in the reversible[5] synthesis of quadricyclanes give no indication of a concerted mechanism which would be postulated on the basis of quantum-mechanical approximations for $_\pi2_s + _\pi2_s$ singlet photoadditions[6]. We have found the reaction to proceed in two steps as illustrated.

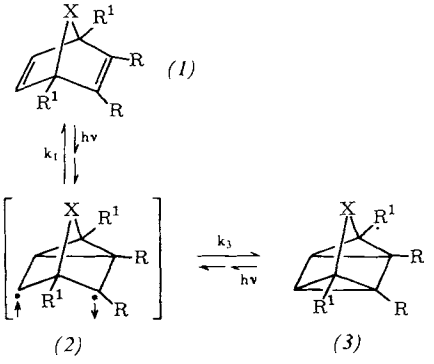
According to this scheme for a nonconcerted reaction, with a (in this case thermally inaccessible[2b, 5]) common intermediate, the sum of the quantum yields for the forward and the reverse reaction should be at most 1. On the contrary, for a concerted mechanism (proceeding *without* a common intermediate) the sum may reach 2[7].

For the case when $\Phi_{forward} + \Phi_{reverse} \leq 1$, the existence of a common intermediate is certain only if other quantum-consuming processes have been taken into account or excluded. Consideration of fluorescence data and a study of possible side reactions are pertinent to this point. On selec-

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tive irradiation, *(1a)* and *(1b)* pass into *(3a)* and *(3b)*, respectively, with quantum yields of 0.55, without fluorescence or phenanthrene formation competing to a detectable extent[2b, 2c, 8] [cf. *(4a)* → *(4d)*, and *(7)* → *(8)*]. Since the



(1)

(2) *(3)*

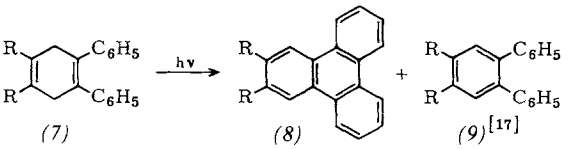
(a), X = CH_2; R = C_6H_5; R^1 = H

(b), X = O; R-R = *o,o'*-$C_6H_4SO_2C_6H_4$; R^1 = H

(c), X = O; R-R = *o,o'*-$C_6H_4OC_6H_4$; R^1 = CH_3

sum $\Phi_{(1)\rightarrow(3)} + \Phi_{(3)\rightarrow(1)}$ is close to unity in both cases it can be concluded that within experimental error all quanta absorbed by *(1)* or *(3)* lead to formation of the intermediate *(2)*, which is deactivated to *(3)* and *(1)* in the ratio k_3/k_1.

the polycycles *(5)* and *(6)* (see Table) and by the photochemical formation of *(8)* from *(7)* (in benzene with O_2 and $5 \cdot 10^{-4}$ mol of I_2 per l)[9].



(7) *(8)* (29%) *(9)*[17] (62%)

R = CO_2CH_3

Further support for the nonconcerted mechanism of quadricyclane formation is provided by the behavior of *(1c)*[10]. This norbornadiene derivative is photolyzed smoothly to *(3c)*[2b, 18], but formation of the intermediate *(2c)* is *not* quantitative (see Table). Accordingly complete intramolecular quenching of fluorescence is not to be expected, and in fact *(1c)* provides an intense emission spectrum (see Table).

Later reports will deal with the consequences of the two-stage singlet process for preparative photochemistry, *e.g.*, the photochemistry of unbridged 1,4-cyclohexadienes[19] such as *(7)*.

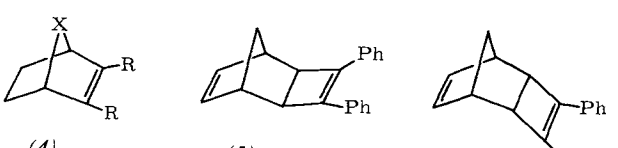
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Table. Kinetic and spectroscopic data [9].

Compound	λ_{max} (nm) [a]	Fluorescence maximum (nm) [b]	Fluorescence yield [c]	$\Phi_{photochem.}$ [d]	$\sum\Phi_{photochem.}$ [e]
(1a) [2c]	304	–	–	0.55	0.9–1.0
(1b) [10]	325 sh, 336, 347 sh	–	–	0.55	1.0
(1c) [10]	311 sh, 326 sh, 343	545, *ca.* 590 sh	0.018	0.02	0.06–0.08
(4a)	291	418	0.005	0.43	
(4b) [10]	297 sh, 310, 325 sh	355 sh, 368, 385 sh	0.22		
(4d)	329, 345, 362 [f]	366, 385, 405, 427 sh, 455 sh [f]	0.41 [f]		
(5) [11]	309, 335 sh	386	0.62		
(6) [12]	305, 311 sh, 330 sh	385	0.52		

[a] Long wavelength band, cyclohexane (sh = shoulder).
[b] Corrected spectra (dQ/dv); standard values in [13].
[c] Relative values, determined planimetrically, and referred to *Berlman*'s new normalized data [14, 15] (9,10-diphenylanthracene, $\Phi_{fl} = 0.83$); 20 °C, degassed cyclohexane.
[d] CH_3CN, 20 °C, bandpass 4.8 nm; *(1)* → *(3)* at 334 or 330 nm; *(4a)* → *(4d)* at 297 nm (isosbestic points: 227, 234.5, 277, 296, 298.5, 304.5, 314, 339 nm).
[e] $\Phi_{(1)\rightarrow(3)} + \Phi_{(3)\rightarrow(1)}$ (253.7 nm, CH_3CN, 20 °C).
[f] 25 °C, degassed CH_3CN.

When formation of the intermediate is prevented by saturation of the unsubstituted double bond in *(1)*, then both the expected intense fluorescence and, in the case of *(4a)*, the very rapid formation of the phenanthrene derivative *(4d)* are observed (see Table).



(4) *(5)* Ph = C_6H_5 *(6)*

(a), X = CH_2; R = C_6H_5

(b), X = O; R-R = *o,o'*-$C_6H_4SO_2C_6H_4$

(d), X = CH_2; R-R = *o,o'*-$C_6H_4C_6H_4$

Fluorescence and (dihydro-)phenanthrene formation are well documented processes for *cis*-fixed stilbenes[2c, 16], and are further exemplified by the intense fluorescence of

[1] Presented in part at the IUPAC Symposium on Cycloadditions in München (Germany) on 7–10 September, 1970.

[2] a) *G. Kaupp* and *H. Prinzbach*, Helv. Chim. Acta *52*, 956 (1969); b) *G. Kaupp, J. Perreten, R. Leute*, and *H. Prinzbach*, Chem. Ber. *103*, 2288 (1970); c) *G. Kaupp* and *H. Prinzbach, ibid. 104*, 182 (1971).

[3] For example, from the energies of formation of the parent system *(1)*/*(3)* (X = CH_2, R = R^1 = H) [4] and the difference in UV spectra of *(1)* and *(3)* [2] it can be estimated that electronically excited *(3)* should be of higher energy than excited *(1)*, although in most cases no emission transitions could be assigned because of absence of fluorescence.

[4] *R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn*, and *M. Pomerantz*, J. Amer. Chem. Soc. *90*, 4315 (1968).

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[7] Apparently no reversible photoisomerizations have yet been reported in which the limiting value of 1 has been significantly exceeded, although this could also occur when the forward and reverse reactions proceed by different mechanisms.

[8] Further, no fluorescence is at first observed on 253.7-nm irradiation of *(1a)* and *(1b)* or *(3a)* and *(3b)* although indistinctly fluorescing by-products are formed on prolonged irradiation.

[9] All the new compounds were characterized by elemental analysis and spectroscopic techniques.

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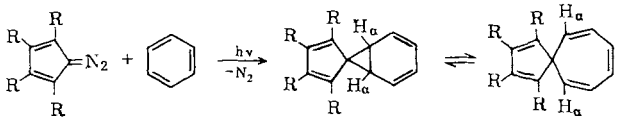
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New Spironorcaradienes. — Demonstration of a Reversible Norcaradiene-Cycloheptatriene Valence-Isomerization[**]

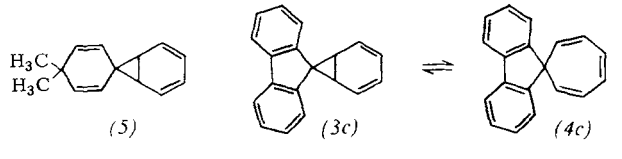
By *Heinz Dürr* and *Helge Kober*[*]

Some time ago[1,2] we postulated that spiro-norcaradienes or -cycloheptatrienes occur as intermediates in the photolysis of unsubstituted or substituted diazo-cyclopentadienes in benzene. In the meantime two relatively unstable spiro-norcaradienes [*(3a)* and *(5)*] have been synthesized[3,4].

(3)⇌*(4)*	Yield (%)	$\Delta H^0_{(3)} - \Delta H^0_{(4)}$ (kcal./mole)	$\Delta S^0_{(3)} - \Delta S^0_{(4)}$ (cal. deg^{-1} mole^{-1})
(a), R=H	30–40 [4]	–	–
(b), R=Cl	30	+0.994	+4
(c)	8–10	+0.45	+2



(1) *(2)* *(3)* *(4)*



(5) *(3c)* *(4c)*

This paper describes the synthesis of a stable spiro-norcaradiene *(3c)* which is in equilibrium with its valence isomer the spiro-cycloheptatriene *(4c)*. The less stable *(3b)*⇌*(4b)* has also been prepared.

The valence tautomers *(3)*⇌*(4)* can be synthesized very easily by photolysis of diazo-cyclopentadienes *(1)* in benzene *(2)* at 17–20°C using a Hg high pressure lamp.

(3c)⇌*(4c)* is so stable that it can be purified by chromatography on basic aluminum oxide at ordinary temperatures (see [1,2]). Pure *(3c)*⇌*(4c)* in C_6D_6 can be kept at 100°C for 10 hours without decomposition. *(3a)*⇌*(4a)* isomerizes at room temperature within 24 hours[1,2]. The complete isomerization of *(3b)*⇌*(4b)* takes about 15 hours at 37°C.

Proof of structure is based on elementary analysis and, mainly, on spectroscopic data[1,2]. The equilibrium between the valence isomers *(3)* and *(4)* is established unequivocally by temperature dependent NMR spectra. The spectrum of *(3c)*⇌*(4c)* in CS_2 at 40°C shows the following signals: $\tau = 5.26$ (2 H/d), $J = 9.2$ Hz; 3.84 (4 H/m); 2.86 ppm (8 H/m). The doublet begins to broaden at −60°C and gives a very broad signal at −80°C. At −90°C new signals appear at $\tau = 4.8$ and 3.0 ppm, which at −100°C give rise to a broad singlet at 6.98 and a doublet at 4.77 ppm ($J = 9.5$ Hz). These signals can be assigned to the H_α-protons[5] of *(3c)* and *(4c)*, respectively. On rewarming to room temperature the original spectrum appears again. The same holds for *(3b)*⇌*(4b)*. It can be concluded from the chemical shift of the H_α-protons of the known compounds *(3a)* and *(5)* that here, too, a fast equilibrium (on the NMR time scale) exists[3–5]. Thus it is proved[5] that the spiro-compounds *(3)*⇌*(4)* undergo a fast reversible valence isomerization. Evaluation of the temperature dependent NMR-spectra[5] allows calculation of the enthalpy and entropy differences of the valence tautomers *(3)*⇌*(4)* (see Table).

Spiro[fluorene-9,7'-norcaradiene]⇌*Spiro[2,4,6-cycloheptatriene-1,9'-fluorene] (3c)*⇌*(4c)*

A solution of diazofluorene *(1c)* (10.0 g) in distilled benzene (350 ml) was photolyzed at room temperature (17–20°C) with a Philips HPK 125 W lamp (Pyrex filter). After 4 hours 80% conversion was achieved (N_2 evolution). Benzene was evaporated *in vacuo* and the residue extracted 3 times with petroleum ether (b. p. 40–80°C). After evaporation of the petroleum ether the residue was subjected to chromatography on 250 g of basic aluminum oxide. Petroleum ether eluted 800 mg (8%) [based on reacted *(1c)*] *(3c)*⇌*(4c)* as colorless crystals; m.p : 98—99°C (from ether/pet. ether); thin-layer chromatography showed only one spot; IR (KBr): 1476(w), 1454(s), 1092(m), 1042(w), 1038(w), 804(s), 791(s), 743(s), 728(s) cm^{-1}; UV($CHCl_3$): $\lambda_{max}(\varepsilon) = 302(4230)$, 287(6870), 262(11990); Raman spectrum (solid): 1554 cm^{-1} (norcaradiene band).

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Tetrakis(trimethylphosphane)cobalt(0): Preparation and Reactions

By *Hans-Friedrich Klein*[*]

Only occasional complexes of zerovalent cobalt with phosphane ligands have been described so far[1, 2]. Attempts to prepare them often gave, instead, phosphane-substituted cobalt hydrides of the type $(R_3P)_4CoH$[3]. Since the CoH stretching vibration of these compounds absorbs more or less strongly according to the nature of the phosphane ligands and in some cases cannot be observed at all, the possible existence of phosphane-substituted cobalt(0) complexes under any conditions has been placed in doubt in very recent publications[3].

However, we have been able, for the first time, to obtain paramagnetic tetrakis(trimethylphosphane)cobalt(0) *(1)*, by reduction of anhydrous cobalt halides with sodium amalgam in presence of trimethylphosphane.

$$CoX_2 + 4\ (CH_3)_3P + 2\ Na(Hg) \xrightarrow[20\,^\circ C]{THF} [(CH_3)_3P]_4Co + 2\ NaX$$

(1)

After removal of volatile materials from the reaction mixture, the compound *(1)* was extracted with hexane; it crystallized at −50 °C or was sublimed at 80 °C/1 torr. In an atmosphere of nitrogen the dark brown needles decompose only at 180–185 °C and they dissolve very readily in hydrocarbons, ethers, or other apolar solvents. Cryoscopic determinations of molecular weight in benzene gave the simple formula weight. Thus in solution *(1)* shows little of the tendency to dimerize that is observed with, for instance, $Co(CO)_4$[4] and $Co(PF_3)_4$[5]. In accordance with this, NMR-spectroscopic determination of the paramagnetic susceptibility[6] (in benzene containing 5% of cyclohexane, at 30 °C) gave a magnetic moment μ of 1.70 B. M., as expected for the d^9 configuration in a tetrahedral ligand field.

The intense EPR signal[7] (at 77 °K, 1% in a toluene matrix) shows complex hyperfine structure caused by the cobalt nucleus with $I = 7/2$. The total of 16 lines corresponds to the two g factors that are expected under these conditions and they imply Jahn-Teller distortion of the tetrahedron. These details must be studied at still lower temperatures.

In the absence of a catalyst, *(1)* does not react with molecular hydrogen. However, if *(1)* is synthesized by the above reaction in a H_2 atmosphere the *(1)* produced is accompanied by some $[(CH_3)_3P]_4CoH$[8] which becomes the main product after 8 hours' reaction.

Solutions of *(1)* rapidly absorb one equivalent of nitric oxide with formation of diamagnetic nitrosyltris(trimethylphosphane)cobalt *(2)*.

$$(1) + NO \longrightarrow [(CH_3)_3P]_3CoNO + (CH_3)_3P$$

(2)

The compound *(2)* crystallizes as slightly sensitive red needles (m. p. 107–108 °C, from hexane) and can be sublimed without decomposition at 60–65 °C/1 torr. The NMR spectrum shows pseudotriplet structure for the $(A_9X)_3-C_{3v}$ system of the phosphane ligands, $|J_{AX} + J_{AX'}| = 5.8$ Hz[9]. In the IR spectrum the NO stretching vibration at 1605 cm^{-1} is at the longest wavelength so far observed for compounds of the type $L_3Co(NO)$[10].

The compound *(1)* reacts with azobenzene analogously to tetrakis(trimethylphosphane)nickel(0)[11, 12], giving a quantitative yield of azobenzenebis(trimethylphosphane)-cobalt *(3)*, which forms dark violet leaflets, m. p. 126–127 °C (dec.), from tetrahydrofuran.

$$(1) + C_6H_5\text{-}N{=}N\text{-}C_6H_5 \longrightarrow \begin{matrix} C_6H_5\text{-}N & P(CH_3)_3 \\ \| \rightarrow & Co \\ C_6H_5\text{-}N & P(CH_3)_3 \end{matrix} \quad (3) + 2\ (CH_3)_3P$$

The IR spectrum of *(3)* differs only slightly from that of the analogous nickel complex in the positions and intensities of the bands. This finding, together with the result of magnetic measurements [$\mu = 2.02$ B. M. for *(3)*], indicates coordination of the cobalt only to the azo group, without an additional σ-bond to the *ortho*-position of a benzene ring[13].

It is thus shown that not only are paramagnetic cobalt(0) compounds with phosphane ligands surprisingly stable, but also that they are amenable to replacement reactions with retention of their paramagnetic valence state.

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Restricted Rotation in *N*-Silylated Hydrazines

By *Otto Josef Scherer* and *Uwe Bültjer*[*]

In continuation of our investigations concerning restricted rotation around sulfur-[1], arsenic- and antimony-nitrogen[2] bonds in compounds containing as ligand to nitrogen an organic derivative of a Group IV b element, we have studied *N*-silylated hydrazines of type *(1)*.

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For their replacement we used both a double reaction of metalated *N,N'*-dimethylhydrazine with organosilicon halides and fission of Si—N bonds by $(CH_3)_2SiX_2$ compounds.

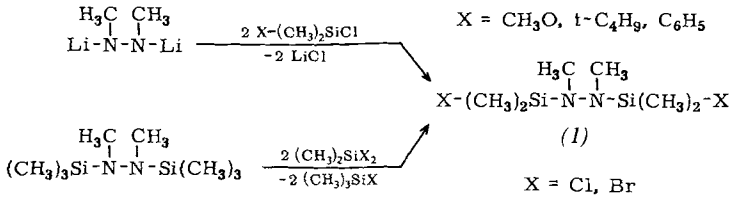


Table. Physical properties and ^{1}H-NMR data (60 MHz; 20% solution in toluene) of *N*-silylated hydrazines *(1)*.

(1)	X	B. p. (°C/torr)	$\nu(CH_3)_2Si$ (Hz)	T_c (°C)[a]	$\Delta G^{\neq}_{T_c}$ (kcal/mole)
(a)	CH_3O	74–78/5			
(b)[b]	$(CH_3)_2N$	81–84/3			
(c)	*tert*-C_4H_9	98–100/0.7			
(d)	C_6H_5	120–121/0.07	2.5	7	15.4 ± 0.3[c]
(e)	Cl	46–47/1 [3]	3.7	47	17.4 ± 0.3
(f)	Br	60–61/0.5	4.2	42	17.1 ± 0.3

[a] ±2°C.
[b] *(1b)* was prepared from *(1e)* and dimethylamine.
[c] Since the width of the $(CH_3)_2Si$ signals at height is 2.0 Hz one must correct the values according to [6]; we have $k_c = 3.0$ and $\Delta G^{\neq}_{T_c} = 15.7 \pm 0.3$.

In contrast to hydrazine derivatives containing $C_6H_5CH_2$ or $(CH_3)_2CH$ groups[4], the compounds *(1)* permit for the first time a systematic variation of the ligand serving as probe in dynamic ^{1}H-NMR spectroscopic studies. In the spectra of *(1a)*—*(1c)* the protons of the CH_3 groups bound to the Si atom are isochronous not only at different concentrations and in various solvents (chloroform to −40°C, chlorobenzene to −30°C, benzene to 10°C, ethylene dichloride and *o*-dichlorobenzene to 20°C) but also in toluene to −75°C, which contraindicates that the chemical shifts of the two CH_3 signals are accidentally equivalent; however, for *(1d)*—*(1f)* they remain anisochronous [$(CH_3)_2Si$ doublet] in various solvents and at various concentrations. This might be due to hindered rotation around the N—N or Si—N bond or to an N-inversion that is slow on the NMR time scale. The latter can be excluded by the $\Delta G^{\neq}_{T_c}$ values (see Table), especially as an N-bound silyl group decreases the inversion barrier[5] by flattening the nitrogen pyramid (cf. also [2]). Hindered rotation around the Si—N bond is unlikely because the compound

$(CH_3)_2N—N(CH_3)Si(CH_3)_2Cl$

—if N-inversion is rapid only Si—N and not N—N hindered rotation can be recognized in the ^{1}H-NMR spectrum —shows only one signal for the $Cl(CH_3)_2Si$ group in toluene down to −75°C[7].

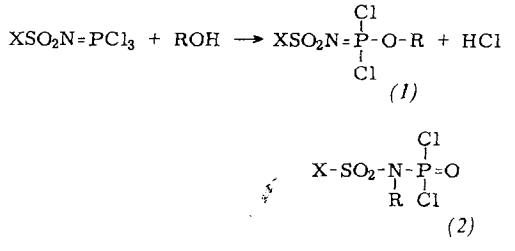
The height of the energy barrier to N—N rotation in *(1)* is apparently influenced by electronic and not by steric effects. This became clear because restricted rotation around the N—N bond of compounds *(1d)*—*(1f)* could be demonstrated only with ligands (X = Cl, Br, or C_6H_5) that are electron-attracting in aliphatic or aromatic compounds. Further, the $\Delta G^{\neq}_{T_c}$ values increase parallel to the increase in (−*I*) effect of the ligands X = Cl, Br, and C_6H_5.

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A Novel Rearrangement around the (P=N) Double Bond[1]

By *Herbert W. Roesky* and *Walter Grosse Böwing*[*]

Trichloro-*N*-(fluorosulfonyl)iminophosphorane or the *N*-(chlorosulfonyl) analog reacts with an equivalent amount of methanol or ethanol in methylene dichloride to yield alkyl dichloro-*N*-(halosulfonyl)iminophosphates *(1)*.



			B. p. (°C/torr)	Yield (%)
(a)	X = F, R = CH_3	*(2a)*	29°C/0.1	90
(b)	X = F, R = C_2H_5	*(2b)*	31°C/0.01	95
(c)	X = Cl, R = CH_3	*(2c)*	58°C/0.01	95
(d)	X = Cl, R = C_2H_5	*(2d)*	68°C/0.01	80

The compounds *(1)* can be obtained in high yield but cannot be distilled without decomposition; they can be characterized by their NMR spectra and by elemental analysis. No ^{1}H-^{19}F coupling was observed for *(1a)* or *(1b)*. The ^{1}H- and ^{19}F-NMR spectra afford the following data for *(1a)*:

$\delta_H = -4.46$ ppm (doublet), $J_{H-P} = 17.5$ Hz, $\delta_F = -58.7$ ppm (doublet), $J_{F-P} = 4.5$ Hz.

Migration of the alkyl group has not hitherto been observed on alcoholysis of trichloroiminophosphoranes[2].

If the compounds *(1)* are heated in diethyl ether or dioxane, they rearrange to *N*-alkyl-*N*-(halosulfonyl)aminodichloro-

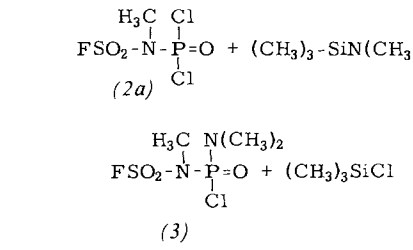
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[1] *O. J. Scherer* and *R. Schmitt*, J. Organometal. Chem. *16*, P11 (1969).
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phosphoric esters *(2)*. Compounds *(2a)*—*(2d)* are colorless liquids which, unlike their isomers *(1)*, distill unchanged in an oil-pump vacuum. For *(2a)* a coupling between ^{19}F and ^{1}H is observed and from the NMR spectra of this compound one obtains $\delta_H = -3.77$ ppm (2 doublets), $J_{H-P} = 10.8$ Hz, $\delta_F = -52.9$ ppm (2 quadruplets), $J_{F-P} = -4.5$ Hz, $\delta = -6.2$ ppm (2 quadruplets) [external standard: $(CH_3)_4Si$, $CFCl_3$, or 85% H_3PO_4]. The structures of the chlorosulfonyl derivatives could be confirmed by mass spectrometry: for *(2c)* there were observed, besides the molecule ion 245 (6%), the characteristic fragments at $m/e = 244$ [$FSO_2NCH_2POCl_2$ (6%)], 210 [FSO_2NCH_3POCl (100%)], 146 [NCH_3POCl_2 (91%)], 130 [NCH_3PCl_2 (36%)], 128 [$ClSO_2NCH_3$ (26%)], and 117 [$POCl_2$ (74%)]. This reaction can be applied to other (P=N) double bonds.

It was not possible to differentiate the (P=N) stretching vibration of *(1a)* and the (P=O) stretching vibration of *(2a)* in their IR spectra. For *(2a)*, bands were observed at *ca.* 2960 s, 1450 vs, 1425 vs, 1290 vs, 1220 vs, 1050 vs, 910 vs, 805 vs, 695 vs, 600 vs, 560 vs, 530 s, 515 vs, 455 m, and 400 s (cm^{-1}).

Compounds *(2)* cannot be prepared from *N*-(halosulfonyl)alkylamines and phosphorus trichloride in the presence of a tertiary amine. Compound *(2a)* reacts with $(CH_3)_3SiN(CH_3)_2$ in 1:1 molar ratio with loss of chlorotrimethylsilane:



(2a)

(3)

The product *(3)* distills unchanged at 59 °C/0.01 torr.

Preparation of (2a):

$FSO_2N{=}PCl_3$ (0.1 mol) is dissolved in CH_2Cl_2 (500 ml). Then the flask is cooled in ice, and CH_3OH diluted with CH_2Cl_2 (250 ml) is dropped in slowly with stirring. When addition is complete, the mixture is boiled under reflux for an hour, to complete removal of HCl. Finally diethyl ether (50 ml) is added and the whole is heated for about 20 minutes under reflux. The ether and CH_2Cl_2 are removed in a vacuum and the residue is distilled in an oil-pump vacuum. Yield: 21 g (90%). *(2b)* is formed as by-product.

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CONFERENCE REPORTS

Macromolecular Colloquium

The Macromolecular Colloquium was held at Freiburg/Br. (Germany), February 25—27, 1971

From the lectures:

Detection of Grafting and Crosslinking of the Elastomer Phase in Two-Phase Systems

By *Lothar Bohn*[*]

It is well known that the toughness of brittle, hard materials can be improved by the incorporation of a finely divided soft phase. As an essential condition for the effect of the rubbery soft phase, it is always plain that the two immiscible polymer phases must be strongly bonded at the contact surface. Some crosslinking in the rubber phase is sometimes also regarded as important. Attempts are made to achieve adhesion between the phases, *e.g.* by graft copolymerization, polymer chains corresponding to the hard basic component being grafted onto a previously prepared rubber latex.

The method normally used in the past for the determination of the grafting and crosslinking state in such a material consists in breaking it down by trying to bring it into solution, and then determining the insoluble fraction and its swelling behavior and composition.

It will now be shown that information on grafting and crosslinking can also be obtained in the original material in the solid state. The difference in shrinkage of the glass and rubber phases on cooling from the melt can lead to "thermal stress", which affects the glass transition of the elastomer phase. This is discussed for the case of rubber-modified styrene/acrylonitrile copolymers (ABS). The importance of the "thermal stress" to the fracture mechanism, particularly to the initiation of crazing, is also discussed.

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Thermodynamics of the Cooperative Transformations of Biopolymers in Solution

By *Th. Ackermann*[*]

One of the characteristics of typical biopolymers is that the thermal transformation process from a highly ordered

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secondary structure into the random coil arrangement, which can take place in solvents with suitable compositions, proceeds almost to completion within a relatively narrow temperature range. Some calorimetric methods for the determination of transformation enthalpies are also suitable for the direct determination of the degree of transformation as a function of the temperature.

This method is discussed in connection with the thermodynamic stability parameters characteristic of the cooperative transformations.

The transformation curve derived from these thermodynamic measurements is compared with the transformation curves obtained by optical and spectroscopic measurements for a number of examples (polynucleotides, polypeptides).

Association Behavior of Atactic and Stereospecific Polymethyl Methacrylates

By *Werner Borchard* (lecturer), *Manfred Pyrlik*, and *Günther Rehage*[*]

The stereocomplex formation observed in mixtures of stereospecific polymethyl methacrylates (PMMA) in some solvents has been investigated over a wide temperature range by viscometric and NMR spectroscopic methods. It is shown with the aid of viscosity and swelling measurements that the association of various stereospecific molecular regions also occurs in atactic and crosslinked PMMA. It can be deduced from the temperature dependence of the reduced specific viscosity and of a number of swelling curves that the stereocomplexes of different sizes are formed in the same temperature range. In dilute solutions prepared from mixtures of isotactic and syndiotactic PMMA and toluene, one observes behavior that can be explained by association that takes place mainly between coils. The observed anomalies in very dilute solutions of atactic PMMA can be explained by association within a coil. No solutions or gels in chloroform exhibit any unusual behavior.

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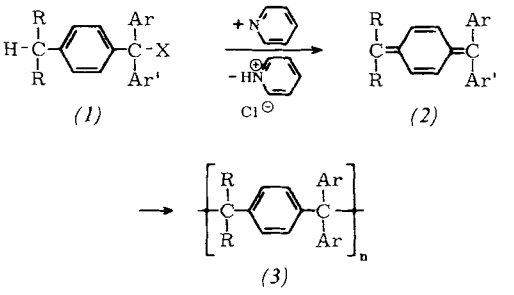
Aromatically Substituted Poly-*p*-xylylenes

By *Dietrich Braun* (lecturer) and *Ulrich Platzek*[*]

The preparation and polymerization of 1,4-α,α-diarylquinodimethanes were investigated in the course of studies on stable polyradicals.

The polymers obtained from 4-alkyltriphenylmethyl halides *(1)* and pyridine have a polydiarylxylylene structure *(3)*.

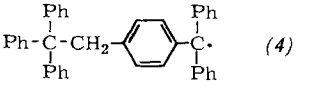
The reaction mechanism was elucidated with the aid of ESR spectroscopy for 1,4-α,α-diphenylquinodimethane *(2)*, R = H, Ar = Ar′ = phenyl. The polymerization is initiated by 4-methyltriphenylmethyl. The ESR spectra change



(1) *(2)* *(3)*

Ar = phenyl, *p*-tolyl
Ar′ = phenyl, *p*-tolyl, *o*-tolyl, α-naphthyl
R = H, CH_3
X = Cl, Br

as the polymerization proceeds, until only macroradicals having structures comparable with that of the model radical *(4)* are present.



(4)

4-Alkyltriphenylmethyls have also been detected as initiator radicals in the case of the other quinodimethanes.

The polymers can be separated by gel chromatography on polyvinyl acetate gels (Merckogel). The polyxylylenes obtained by free-radical reactions have relatively low molecular weights.

Determination of Sequence Length Distributions from the Pyrolysis of Labeled and Unlabeled Ethylene-Propylene Copolymers

By *Josef Exner*, *Michael Seeger*, and *Hans-Joachim Cantow* (lecturer)[*]

The properties of copolymers depend not only on their overall composition, but also on the distribution of the different sequences from which they are built up. The report deals with attempts to calculate the distribution of the sequences in ethylene-propylene macromolecules from the distribution of fragments obtained by thermal degradation of the copolymers.

The use of pyrolysis in investigations of this type depends on the reappearance of essential structural features of the polymer chain in the pyrolysis products. This is particularly likely to occur if the pyrolysis is carried out in such a way as to favor the formation of longer fragments. We therefore used depolymerization under a hydrogen atmosphere, with the pyrolyzer coupled to a temperature-programmed gas-chromatographic separating column[1, 2].

To allow an independent check on the sequence length distributions calculated from the experimental fragment distribution on the assumption of plausible cleavage mechanisms, we prepared copolymers with sequence structures

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that could be precalculated from the kinetics of polymerization. A very reliable calculation of the distribution of ethylene sequences from that of the linear fragments is possible if one simply assumes the superposition of preferential α-cleavage at the tertiary carbon with random cleavage in the ethylene sequences[1, 3]. Cleavages leading to isoalkanes are also discussed. It is shown that the sequence length distributions obtained do not depend critically on the conditions of pyrolysis and of separation.

Radio gas chromatography of the fragments from labeled copolymers considerably increases the accuracy of the analytical results. For this purpose we prepared copolymers with definite structures labeled on the α-CH_3 with tritium, and subjected the pyrolysis products to parallel determination of the carbon content with a flame ionization detector and determination of the activity with a radiation detector.

Among other things, it was found that the *n*-alkanes were active. The cleavage at the tertiary C atoms thus takes place in the chain. The activity of the *n*-alkanes in relation to their mass is roughly inversely proportional to their chain length. However, the intensities of the two greatest "iso-signals", which overlap, differ in their ratio according to the detector used. This provides information about the structure and the cleavage mechanisms of the intersequence cleavage fragments.

It appears possible to analyze the sequence structures even of terpolymers with relatively low contents of the third component.

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Determination of the Polydispersity of Anionic Polystyrenes by Phase Distribution Chromatography (PDC)

By *R. H. Casper* (lecturer) and *G. V. Schulz*[*]

For the phase distribution chromatography of polystyrene, glass spheres coated with a thin film of high molecular weight polystyrene ($M = 8 \times 10^6$) are packed into a thermostated metal column (VA steel) together with cyclohexane. The polymer film swells to form a gel layer about 3000 Å thick. The polymer sample to be fractionated, whose average degree of polymerization should be about one order of magnitude lower than the degree of polymerization of the polymer film, is dissolved in cyclohexane and injected at the top of the column. The sample is then washed through the column with pure cyclohexane.

The migration of the polymer through the column can be formally described by the model of a liquid/liquid partition chromatography. Each degree of polymerization P distributes itself according to its partition coefficient $K(P)$ (ratio of the concentrations of the polymer P in the gel and in the sol phase respectively) between the stationary gel phase and the mobile sol phase. $K(P)$, and hence the elution volume, increases with falling temperature and increasing degree of polymerization. The elution volume $V_e(P)$ depends on P in accordance with the following equation:

$$V_e(P) = V_e^0 \left[1 + \frac{K(P)}{r_v} \right] \quad (1)$$

r_v = ratio of the volumes of the sol and gel phases;
V_e^0 = volume of the total sol phase in the column.

On the assumption that the two phases are in equilibrium, it is possible to determine $K(P)$ from $V_e(P)$. $K(P)$ can be calculated independently on the basis of the Flory-Huggins equation for the case of phase equilibrium. The thermodynamically calculated values agree well with the values obtained by chromatography. It can be shown both theoretically and experimentally that the dependence of the partition coefficient on P can be described by the equation:

$$K(P) = \exp(\varepsilon \cdot P) \quad (2)$$

which was used by *Brønsted* and by *Schulz*. It can therefore be concluded that the retention results from partition of the polymer between two liquid phases, and that the chromatography takes place at least approximately under equilibrium conditions.

The width of the elution curve of a polymer mixture depends on the breadth of the molecular weight distribution, as well as on the column temperature and the average degree of polymerization. Conversely, if the dispersion broadening and the type of molecular weight distribution (Poisson, Gauss, or Schulz distribution) are known, the polydispersity of the sample can be determined from the breadth of the elution curve. This assumes that the polymers pass through the column independently of one another. Under the further (experimentally verifiable) assumption that the concentration profile of a single component P on leaving the column can be described by a bell-shaped Gauss curve with variance σ, the elution curve of a polydisperse mixture with the differential mass distribution $H(P)$ is given by the equation

$$C(V) = f \int_0^x H(P) \cdot \exp\left[-\left(\frac{V - V_e^0\left(1 + \frac{K(P)}{r_v}\right)}{\sigma\sqrt{2}} \right)^2 \right] \cdot dP \quad (3)$$

(f = normalization constant). $C(V)$ is the concentration of the polymer in the eluate. According to equation (3), the variance σ_v of the elution curve $C(V)$ can be calculated for a given distribution $H(P)$ if V_e^0, σ, and ε are given, and this value can be compared with the variance of the elution curve found experimentally for a product having the same average degree of polymerization. The polydispersity of the polymer mixture is finally found from this comparison.

Measurements on anionic polystyrene samples showed that the polydispersities calculated from σ_v agree, to within the limits of accuracy, with the values found by gel chromatography and (in some cases) by Baker-Williams fractionation.

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Stereochemical Control in Free-Radical Polymerizations

By *Hans-Georg Elias* (lecturer) and *Paul Göldi*[*]

No simple relationships between the constitution of a monomer and the tacticity of a polymer prepared by a free-radical reaction are known so far. For example, the

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direct comparison of the syndiotacticity of polymers prepared at the same temperatures and also parameters indicating deviations from Bernoulli statistics have failed. On the other hand, the quantities T_0 and $\Delta\Delta H_0^*$, which can be determined from the temperature and solvent dependence of the ratio of the mole fractions of isotactic and syndiotactic diads formed in the polymerization, have been found to be suitable. The compensation temperature T_0 is the temperature at which the effects of the solvents just compensate one another so that the same tacticity is always obtained, irrespective of the solvent. Linear relations exist between T_0 and $\Delta\Delta H_0^*$ both for vinyl and for acrylic monomers. In the series of vinyl monomers, T_0 also depends on the size of the substituents and their interaction.

"Molecular Probes" in the Study of Polymer Structure and Interactions

By *J. E. Guillet*[*]

Recent experiments in our laboratories have shown that the technique of gas chromatography may be utilized to obtain extensive information about polymer structure and interactions in the solid phase. Although it might appear logical to apply the name "gas chromatography of polymers" to such experiments, the terminology is misleading in that the polymer is obviously not in the gas phase, nor is it undergoing a chromatographic separation. In fact the nature of the experiment has more in common with the molecular beam technique for gaseous reactions and we prefer therefore to refer to these as studies on polymers using "molecular probes".

In essence, the experiment involves sending a pulse of molecules along a narrow tube which has a thin coating of the polymer to be investigated covering the inner wall or on the surface of a suitable inert support. The probe molecules will undergo random diffusional motion in all directions, upon which is superimposed a velocity U in the forward direction maintained by a flow of inert carrier gas. In general each of the probe molecules will have a velocity component U_p perpendicular to the flow direction which will cause them to impinge on the polymer surface at the wall. If there is no interaction with the polymer there will be no alteration in the component of velocity U_f in the forward direction. On the other hand any interaction with the polymer will result in a retardation of the net translational velocity of the probe molecules along the tube direction. The strength and nature of the interaction can be deduced from this change in velocity by application of rather simple physicochemical considerations.

The use of hydrocarbon probes such as decane and hexadecane in an inverse chromatography experiment employing various polymers as stationary phases is described. It is shown that the crystalline regions of such polymers are impermeable to the probe molecules and hence the degree of crystalline order can be estimated solely from chromatographic retention data. Estimates of diffusion constants and glass transition may also be obtained.

Studies were also made of polymer transitions occurring isothermally. Using an automated injection apparatus the rate of crystallization of several samples of polyethylene and polypropylene were determined at a series of temperatures. The results agree well with data published on similar polymers obtained by dilatometric methods.

Studies of glassy polymers such as polystyrene, poly(methyl methacrylate) and polyvinylchloride show clear evidence for other transitions, such as T_g, involving changes in polymer segment mobility.

The basic expressions of gas-liquid chromatography relate the solute activity coefficient to an experimental specific retention volume. Application of these equations to polymer-containing systems is complicated by the need to define a suitable molecular weight for the polymer. The difficulty is overcome by considering the solute activity, which can be related to the experimental retention volume, without the explicit knowledge of the polymer molecular weight. Statistical thermodynamics of polymer solutions have been applied to this case, showing that experimental retention volume data may be used directly to calculate solute-solvent thermodynamic interaction parameters. These parameters can be expressed in terms of conventional Flory-Huggins concepts, leading to characteristic values of the κ parameter as illustrated for the case of *n*-alkane/polyethylene.

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Oligomerization of Ethylene

By *G. Henrici-Olivé* (lecturer) and *S. Olivé*[*]

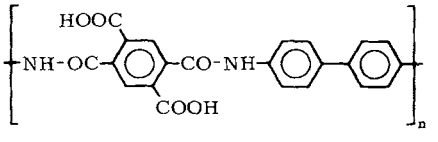
The oligomerization of ethylene on systems based on Ti(IV) and alkylaluminum compounds is described as an example of catalyst tailoring in homogeneous catalysis. The lecture deals with the systematic investigation of the relations between the nature of the ligands on the Ti or Al side of the catalytic complex and the properties of the product (position of the double bonds, chain length, and degree of branching of the oligomer). As a result of the findings, it is possible to direct the oligomerization in such a way as to obtain predominantly short-chain, linear α-olefins.

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Influence of Triethylamine on the Viscosity of Poly(amic Acids) from Pyromellitic Dianhydride and Benzidine in Dimethylacetamide

By *A. Horvath* (lecturer) and *Bruno Vollmert*[*]

Aromatic poly(amic acids) (PAA) are structurally interesting because of their relatively immobile aromatic structural units, which may be expected to have a chain-stiffening effect. This effect is particularly pronounced when benzidine is used as the diamine component in the synthesis:



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On addition of triethylamine (TEA) to the dilute solutions of PAA in dimethylacetamide (DMA), the reduced specific viscosity η_{sp}/c increases depending upon the molecular weight, the PAA concentration, and the quantity of TEA added, to about twelve times the η_{sp}/c values of TEA-free PAA solutions.

The relatively pronounced increase in viscosity on addition of TEA is attributed to opening up of the coils by the intramolecular interaction of the carboxylate ions. The ions are formed by protonation of the TEA in accordance with the following equation:

$$R\text{-}COOH + N(C_2H_5)_3 \rightleftharpoons R\text{-}COO^{\ominus} + HN^{\oplus}(C_2H_5)_3$$

The η_{sp}/c values decrease with increasing PAA concentration, as is also found in aqueous solutions of polyelectrolytes. In contrast with the viscosity-titration curves of aqueous polyelectrolyte solutions, the η_{sp}/c values do not pass through a maximum with increasing addition of base, but move asymptotically toward certain limiting values. This behavior is due to the fact that the neutralization of the PAA is carried out here in an aprotic solvent with a base that is incapable of selfdissociation. An excess of TEA favors the formation of ions in accordance with the above equilibrium, but does not itself increase the ionic strength of the solution. The ionic character of the mechanisms proposed is confirmed by suitable electrical conductivity measurements.

Comparison with polymethacrylic acid having the same molecular weight in DMA, for which the increase in viscosity on addition of TEA is much smaller, shows the strong influence of the constitution of the polymer chain, *i.e.* the chain stiffness due to the constitution.

Pyro Field Ion Mass Spectrometry (PFIMS) as an Effective Method for the Determination of the Structure and Degradation Behavior of Polymers and Copolymers

By *Dieter Hummel* (lecturer), *Kurt Rübenacker, Heinz-Jürgen Düssel*, and *Theo Schweren*[*]

In PFIMS, the sample (a few µg) is pyrolyzed isothermally or in accordance with a temperature program in a gold crucible at a distance of about 5 mm from a Pt ionizing wire (2–4 µm, +8000 V). Only slight additional fragmentation occurs on ionization of the molecule-fragments on the emitter filament. An SEM[1] (currents $> 10^{-19}$ A) is used as the collector, and the spectrum is recorded with a direct-recording light (15 s for the range of masses between 10 and 300) or electron beam oscillograph (practically instantaneous).

The behavior of polymers that give large amounts of monomer and oligomers is shown for polyisobutene, polystyrene, polypropylene, and polyacrylonitrile (PAN). Polyvinyl chloride (PVC) is discussed as a particularly characteristic example of the removal of side groups with formation of polyenes and aromatic compounds. Binary copolymers allow a greatly simplified division into three groups, according to their degradation behavior: 1. Preferential rupture at the hetero linkages: breaking out of the sequences. 2. Preferential rupture in the homo sequences of one or both components: formation of characteristic hetero fragments. 3. Smooth rupture both of homo and of hetero linkages: extensive degradation to the monomers (oligomers), no preference for or discrimination against the hetero linkages. Examples discussed include polysulfones (1), vinyl chloride-propylene and α-methylstyrene-acrylonitrile (2), and α-methylstyrene-methyl methacrylate (3).

PFIMS may be particularly useful where a system (homopolymer or copolymer) can polymerize by different mechanisms to give products with different structures. This is shown for the copolymers of vinyl chloride and propylene and for the polymers of vinyl phenyl methylenedisulfone. (The latter investigations were carried out in collaboration with *H. Ringsdorf.*)

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[1] SEM = secondary electron multiplier.

Conformation of Molecules in Undiluted, Noncrystalline Polymers

By *Martin Hoffmann*[*]

In amorphous rubbery polymers the molecules form statistical coils, which penetrate each other and have end-to-end distances $h = \text{const.}\ M^{0.59}$. This result is obtained from the domain sizes in microheterogeneous block copolymers of different molecular weights M, from the light scattering and the diffusion of dissolved molecules in mixtures of polymers, from the intrinsic viscosity, the structural viscosity, and the relaxation modulus of large molecules in smaller ones of the same chemical nature, as well as from the volume contraction in mixtures of polypropylene oxide with solvents. Since important theories[1,2] of the properties of amorphous polymers have hitherto assumed ideal coils ($h = \text{const.}\ M^{0.50}$) or bundled molecules they should be revised.

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[1] *F. Bueche*, J. Chem. Phys. *20*, 1959 (1952); *25*, 599 (1956).
[2] *W. Pechhold*, Kolloid Z. Z. Polymere *228*, 1 (1968).

Formation of Macrozwitterions in the Anionic Polymerization of Vinyl Monomers Initiated by Tertiary Phosphanes

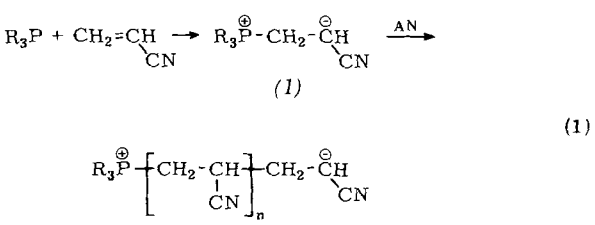
By *G. Franzmann, C. D. Eisenbach*, and *V. Jaacks* (lecturer)[*]

The formation of macrozwitterions *(2)* from acrylonitrile (AN) and a nonionic Lewis base, *e. g.* triethylphosphane [$(C_2H_5)_3P$, formerly called triethylphosphine], in accordance with equation (1) was postulated by *Horner et al.*[1] as early as 1955.

Enikolopyan et al.[2] believed that they had confirmed this by NMR spectroscopic studies. However, our investigations, in which such a polyacrylonitrile was fractionated by fractional precipitation and by gel chromatography, showed

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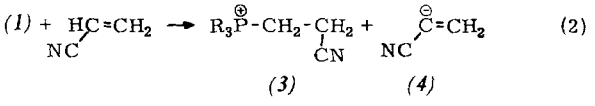
that under the usual polymerization conditions, the zwitterionic chains do not grow beyond a degree of polymerization of 1, even in polar solvents. The large amount of energy required for charge separation is presumably the reason



(1)

(2)

why the chain transfer in accordance with equation (2) occurs and only low molecular weight phosphonium ions *(3)* are formed, whereas the anions *(4)* initiate the chain growth.



(2)

The polymerization of diethyl methylenemalonate $[CH_2=C(COOR)_2]$ with triphenylphosphane in chloroform, on the other hand, proceeds by the zwitterion mechanism corresponding to equation (1). This monomer has no acidic hydrogen that could lead to transfer in accordance with equation (2). The phosphonium groups were detected and determined spectroscopically in the polymer fractions obtained by fractional precipitation and by gel chromatography. The polymers obtained contained almost one phosphonium group per polymer chain.

[1] *L. Horner, H. Jürgeleit,* and *K. Klüpfel,* Liebigs Ann. Chem. *591,* 108 (1955).

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Molecular Weight Distribution of *n*-Component Copolymers ($n \geq 2$) in "Living Polymer" Systems

By *Fritz Horn* and *Joachim Klein* (lecturer)[*]

On the assumption that initiation is complete immediately after addition of the initiator ($k_s \gg k_w$), the chain growth in a living polymer system can be described by equation (1):

$$P_j(v) + M_i \xrightarrow{\varkappa_{ij}} P_i(v+1), \quad i = 1, 2, \ldots n \tag{1}$$

In this equation $P_j(v)$ is a polymer species having the reactive end group formed with the monomer of type j and with a degree of polymerization v; M_i is a monomer of type i in a mixture of n copolymerizing monomers; $\varkappa_{ij}$ is the propagation rate constant for the reaction of a monomer of type M_i with a polymer end group of type j.

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If

$$\mathbf{u}(v,t) = (u^1, u^2, \ldots, u^n)^T \tag{2}$$

is the column vector, which gives the end group concentration of chains having a degree of polymerization v at time t, *i. e.*

$$u^i(v,t) = [P_i(v,t)] \tag{3}$$

and if the monomer concentration is assumed to remain constant, the dynamic equation for the end group concentration is

$$\dot{\mathbf{u}}(v,t) = K\mathbf{u}(v-1,t) - D\mathbf{u}(v,t) \tag{4}$$

where

$$K = \begin{bmatrix} k_{11} k_{12} \cdots k_{1n} \\ k_{21} k_{22} \cdots \\ \cdot \quad \cdot \\ \cdot \quad \cdot \\ \cdot \quad \cdot \\ k_{n1} k_{n2} \cdots k_{nn} \end{bmatrix} \quad \text{and} \quad D = \begin{bmatrix} \sum_{i=1}^{n} k_{i1} & 0 & 0 \cdots 0 \\ & & 0 \cdots 0 \\ 0 & \sum_{i=1}^{n} k_{i2} & \\ 0 & & \cdot \\ \cdot & & \cdot \\ \cdot & & \cdot \\ 0 \cdots & & \sum_{i=1}^{n} k_{in} \end{bmatrix} \tag{5}$$

In this equation, k_{ij} are the pseudo-first order constants for chain growth obtained in accordance with

$$k_{ij} = \varkappa_{ij}[M_i] \tag{6}$$

Solution of the differential equations derived from equation (4) for the first three moments

$$\sum_{v=1}^{\infty} \mathbf{u}(v,t) \cdot v^k, \quad k = 0, 1, 2$$

can provide information on a number of quantities for all times $t > 0$.

These include: 1, the concentration distribution of the end groups as a function of time; 2, the relation of the end group distribution as a function of time to the end group distribution as a function of the chain length (Markoff process); 3, the number average degree of polymerization for classes of species that are characterized by a certain end group, as well as for the material as a whole.

For other quantities that can be derived with the aid of the second moment of $\mathbf{n}$, the treatment of the problem becomes too complex for short times (degree of polymerization). However, valuable information on so-called asymptotic quantities can be easily obtained here.

These quantities include in particular the newly defined dispersion number

$$\lim_{t \to \infty} \frac{\sigma^2(t)}{\bar{v}(t)} = \Theta = \lim_{t \to \infty} (\bar{P}_w - \bar{v}) \tag{7}$$

for which it can generally be proved that $\Theta \geq 1$.

$\Theta = 1$ is valid for the homopolymerization ($n = 1$) and for exceptional cases of copolymerization ($n > 1$). The influence of the monomer concentration, which determines the quantities k_{ij} in accordance with equation (6), on the quantity Θ is discussed in more detail.

Sequence Kinetics in Polymer-Analogous Reactions by Monte-Carlo Simulation and NMR Investigation

By *Ernst Klesper* (lecturer), *Wolfram Gronski*, and *Volker Barth*[*]

If a polymer is subjected to a polymer-analogous reaction, the rate of reaction of the groups to be transformed may depend on the nature of the neighboring groups, *e.g.* on whether the immediately adjacent monomer units have already reacted. Such a cooperative effect of neighboring monomer units causes a deviation of the rates of formation of certain sequences of monomer units from the rates found in the absence of such an effect, *i.e.* in the case of random statistics of the copolymer.

The reaction of a homopolymer to form a binary copolymer was simulated by a Monte-Carlo procedure with a digital computer and by a simple dice method. The model reaction was based on the assumption that the reaction rate constants depend only on whether an unreacted monomer unit is flanked by two unreacted units, only one, or no unreacted monomer unit. The monomer units were called randomly by random numbers, and another random number was used to decide whether the unit had reacted. Alternatively, the monomer units were addressed in order, beginning at the end of the molecule, and reacted as before. It was found that the two procedures were equivalent if the rates of the model reactions were sufficiently low. Counting of the resulting model chains gave relative frequencies for the diads, triads, tetrads, and higher sequences as a function of the number of random numbers or of the conversion.

By suitable choice of the reaction rate constants for the Monte-Carlo simulation, it is possible to obtain a fit to corresponding experimental sequence frequency conversion curves. The ratios of the three experimental rate constants can be determined in this way. It is also possible, with the aid of the simulated model chains, to obtain information about the extent of reversibility of the chains, and whether the frequency even of long sequences can be precalculated with the aid of conditional probabilities of low Markoff order. To characterize the neighboring group effects, even without the determination of the rate constants, conditional probabilities representing the statistical effect of the nearest neighbors in both directions of the chain were introduced. The Monte-Carlo investigation was supplemented by formal-kinetic differential equations for polymer-analogous reactions with three rate constants, which were set up without assumptions.

For the partial hydrolysis of polymethyl methacrylate to methyl methacrylate-methacrylic acid copolymers, reaction conditions were found that led not only to random distribution but also to alternating and block-like distributions of triads. Since all triad frequencies can be determined directly by NMR spectroscopy, this polymer-analogous reaction is suitable for the investigation of the kinetics of the sequences. The alternating structure that results from hydrolysis in aqueous solution with an excess of KOH is due to retarded hydrolysis of monomer units whose neighboring monomer units have already reacted, and hence carry carboxylate groups. On the other hand, the block structure formed with a deficiency of KOH is due to acceleration of the hydrolysis by adjacent monomer units carrying carboxyl groups.

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Reactivity of Pendant Vinyl Groups in Crosslinked Divinylbenzene Polymers and Styrene-Divinylbenzene Copolymers

By *Dietmar Kühnle* (lecturer) and *Werner Funke*[*]

Investigations were carried out on the reactivity of unreacted vinyl groups fixed on the network (pendant vinyl groups) in crosslinked polymers prepared by free-radical polymerization of technical grade divinylbenzene, *p*-divinylbenzene, and styrene/divinylbenzene mixtures. The reagents used were Hg(II) acetate in methanol and *n*-butyllithium in benzene.

The addition of Hg(II) acetate and of *n*-butyllithium to the vinyl groups of the polymer particles was detected by IR spectroscopy. The number of double bonds that reacted in the case of Hg(II) acetate was determined by titration of the acetic acid formed. In the experiments with *n*-butyllithium, ^{14}C-labeled *n*-butyllithium was used, and the conversion was calculated from the radioactivity of the polymer.

Unlike styrene, with which Hg(II) acetate and *n*-butyllithium react in the homogeneous phase, the reactions with the vinyl groups of the crosslinked polymer particles are heterogeneous. The addition of both reagents to the polymer particles consequently proceeds much more slowly than in the case of styrene.

The conversion reaches a final value with sufficiently long reaction times. In the case of Hg(II) acetate, this value often corresponds to quantitative conversion, whereas the reaction with *n*-butyllithium nearly always stops at much lower conversions. The substances investigated differ characteristically in their reaction rates and in their conversions. These differences can be explained by differences in the accessibility of the vinyl groups enclosed in the network. The influence of the reagents, the reaction medium, and the particle structure on the course of the reaction are discussed.

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Monomer Concentration in Polymers and its Correlation with the Polymerization Rate in Heterogeneous Polymerization

By *O. F. Olaj* (lecturer), *J. W. Breitenbach*, *H. Reif*, and *K. J. Parth*[*]

Knowledge of the monomer concentration that prevails in the polymer particles under the conditions of heterogeneous free-radical polymerization should be of great importance to the understanding of the kinetics of heterogeneous free-radical polymerization.

For the experimental determination of the monomer concentration in polyvinyl chloride (PVC) in equilibrium with monomeric vinyl chloride (VC) or with mixtures of VC and the solvent 1,2-dichloroethane (DCE), a method was developed based on the measurement of the increase in the length of massive PVC rods ($[\eta] = 113$ ml/g in cyclohexanone at 25 °C) due to swelling. The relative increase in

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volume $\beta(=\Delta V/V_0)$ due to swelling is 0.42 for swelling in pure VC($c_{VC}=13.6$ mole/l) at 50°C; it increases with increasing addition of DCE, and reaches a value of about 1.85 at a DCE concentration of 5.3 mole/l (corresponding to a VC concentration of 8.3 mole/l) in the swelling agent.

If the volumes are assumed to be additive, the monomer concentrations in the interior of the polymer, c^*_{VC}, can be calculated from the β values for each external concentration c_{VC}. The influence of the preferential absorption of DCE by the polymer was determined by variation of the ratio of swelling agent to polymer. The preference for the solvent DCE is relatively slight. In the range in which the polymerization in the VC-DCE systems proceeds heterogeneously practically from the outset (*i.e.* at c_{VC} between about 8 and 13.6 mole/l), the c^*_{VC} values obtained start at 4.0 mole/l in pure VC, and pass through a maximum with decreasing c_{VC} ($c^*_{VC}=5.3$ mole/l at $c_{VC}=8$ mole/l). This means that the decrease in the VC content of the swelling agent due to the addition of DCE is overcompensated at first by the increase in the uptake of swelling agent by the polymer corresponding to the higher degree of swelling. It is only at relatively high DCE concentrations that c^*_{VC} decreases with decreasing c_{VC}.

The $c^*_{VC}-c_{VC}$ curve has a striking similarity to the $v_{Br}-c_{VC}$ curve for the polymerization of VC under constant initiation conditions, which also passes through a maximum. This leads to a relatively simple formula for the description of the kinetics of the heterogeneous polymerization of VC.

The situation is different in the system polyacrylonitrile (PAN)-acrylonitrile(AN)-dimethylformamide (DMF). PAN($[\eta]=800$ ml/g in DMF at 25°C) is practically unswollen in DMF-AN mixtures up to a DMF content of about 70 vol-%, so that only vanishingly small monomer concentrations can be present in the interior of the polymer. Consequently, the correlation between the polymerization rate and the monomer concentration in the interior of the polymer cannot be so simple as in the system PVC-VC-DCE. The description of the polymerization kinetics here requires complicated formulas that take into account the extremely low monomer concentrations in the interior of the polymer.

Investigations on the Influence of Various Ions on the Radius of Gyration and Structure of tRNA in Solution

By *Ingrid Pilz* (lecturer), *Otto Kratky*, *Friedrich von der Haar*, and *Friedrich Cramer*[*]

Since the primary and secondary structures of many specific transfer ribonucleic acids (tRNAs) are largely known, a series of models for their tertiary structures have been proposed in recent years. The radius of gyration and the scattering curve can be calculated from the atomic coordinates of such a model. These data are compared with the experimental values obtained by X-ray small angle scattering measurements on the molecule in solution.

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During such comparisons the following difficulty must be borne in mind: The experimental investigations are carried out in solution, and little is known about the influence of the ion- and water-shell on the radius of gyration and the structure of a polyelectrolyte such as the tRNAs. Solutions of phenylalanine-specific tRNA from yeast were therefore investigated in the presence of various ions. Only one type of ion was present in each solution. The investigations were carried out on solutions containing Li^+, Cs^+, Mg^{2+}, and Ba^{2+} ions. The influence of the ions was very pronounced. The radius of gyration of $tRNA^{Phe}$ had values of *e.g.* 23.6 Å in the presence of Li^+ ions, 26.2 Å in the presence of Cs^+ ions, and 26.3 Å in the presence of Ba^{2+} ions. These results show very clearly that the influence of the solvent must never be ignored in the comparison of experimental values with data calculated from the atomic coordinates of the molecules.

The melting behavior of the $tRNA^{Phe}$ from yeast was also investigated in the presence and in the absence of Mg^{2+} ions. The melting of the tRNA structure with rising temperature can be followed by the increase in the radius of gyration. In the presence of Mg^{2+} ions, an increase in the radius of gyration was observed at distinctly higher temperatures.

Dielectric Measurements for the Determination of Aggregation and Helix-Coil Transition in Poly-benzyl-L-aspartate and Poly-DL-phenylalanine

By *Eve Marchal*[*]

The dielectric absorption of poly-DL-phenylalanine (PDLPA) and poly-benzyl-L-aspartate (PLAB) was measured in very dilute solutions to determine association and helix-coil transition. Both polypeptides are present as associated helices in chloroform. The mode of aggregation was determined by measurement of the dipole moment and of the critical frequency. The influence of solvent polarity on the aggregates was also investigated in the case of PDLPA.

For both polymers the dissociation of the aggregates in chloroform is observed on addition of a little dichloroacetic acid, while further addition of the acid leads to the helix-coil transition. No second region of dielectric absorption that might be related to the kinetics of the transition occurs during the helix-coil transition of PLAB.

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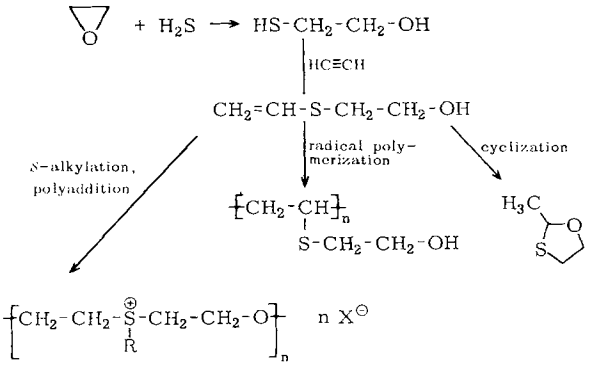
Reactivity, Modification, and Polymerization Behavior of Monomers Containing Sulfur

By *Herbert Naarmann* (lecturer) and *F. J. Feichtmayr*[*]

For the case of 2-hydroxyethyl vinyl thioether, which is readily obtainable by vinylation of 2-mercaptoethanol, relationships are shown between the reactivity of the C=C double bond and the sulfur bridge, which can be converted

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into >SO, $>SO_2$, or $>\overset{\oplus}{S}-$. The scope of the reactions of 2-hydroxyethyl vinyl thioether ranges from the formation of 5-membered rings through free-radical polymerization to polyaddition. The experimental findings agree with HMO calculations on the electron distribution on the vinyl group.



Binary and Ternary Copolymerization in the System Vinyl Chloride-Butadiene-Maleic Anhydride

By *W. Ring*[*]

With free-radical initiation, the addition of small quantities of butadiene to vinyl chloride considerably reduces the polymerization rate in the initial stage. If maleic anhydride is added in small quantities as the third monomer, the polymerization rate increases again.

The accelerating effect of maleic anhydride is not due to a Diels-Alder reaction between maleic anhydride and butadiene. It results instead from modification of the copolymerization process in such a way that the retarding, slow growth step

~butadiene · + butadiene

is suppressed.

Whereas vinyl chloride and butadiene react in accordance with the rules of the conventional kinetics of free-radical copolymerization, the butadiene-maleic anhydride system exhibits a strong tendency toward alternating growth. Vinyl chloride and maleic anhydride, on the other hand, except at extreme compositions of the monomer mixture, form copolymers in which vinyl chloride is present in a molar excess.

The ternary system behaves accordingly. The molar ratio of maleic anhydride: (butadiene + vinyl chloride) in the copolymer is equal to 1:1 only at suitable monomer compositions and/or at low conversions. If these conditions are not satisfied, the copolymers obtained are deficient in maleic anhydride. Nevertheless, the partial conversion of vinyl chloride, taking into account the concentration of butadiene in the monomer mixture, is considerably higher in the presence of maleic anhydride than in the absence of the termonomer.

Reaction mechanisms are proposed, *inter alia*, in the light of recent results obtained by American and Japanese workers for polymerization controlled by donor-acceptor complexes.

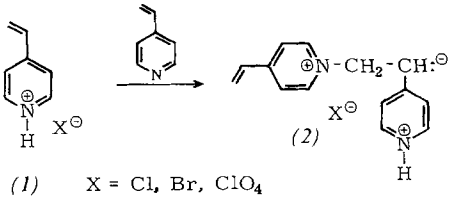
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Mechanism of the "Spontaneous Polymerization" of 4-Vinylpyridinium Salts

By *Ingolf Mielke* and *Helmut Ringsdorf* (lecturer)[*]

4-Vinylpyridinium salts have already attracted wide interest because of their special polymerization properties and the associated considerations on the matrix reaction[1, 2]. The mechanism by which the monomeric salts *(1)* polymerize "spontaneously" during the synthesis or in solution has been formulated by *Kabanov et al.*[2, 3] as a nucleophilic attack of the anion on the strongly activated vinyl group, followed by anionic polymerization.

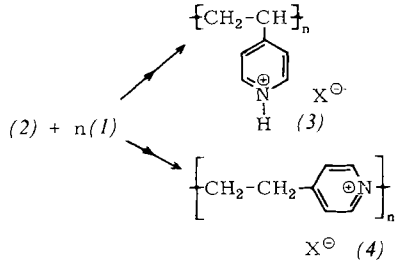
IR and NMR spectroscopic and titrimetric investigation of the reaction course has shown that the polymerization is initiated by 4-vinylpyridine as the nucleophile [eq. (1)][4, 5].



(1)

(1) X = Cl, Br, ClO_4

The course of growth in the polymerization is strongly dependent on the anion, the solvent, and the concentration of the salt[6]. Depending on the reaction conditions, it leads to vinyl polymers having the structure *(3)* or to polyadducts having the structure *(4)*, which have the pyridinium ring in the main chain [eq. (2)].



(2)

According to viscosity measurements on 4-ethylpyridinium salts the change in the reaction mechanism may be due to micelle formation at high monomer concentration and polymerization in the oriented media.

These results also necessitate a check on the course of the "matrix polymerization" of 4-vinylpyridine on polyacids[1].

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The Influence of Proline on the Conformation of a Polypeptide Chain

By *Manfred Rothe* (lecturer), *Rainer Theysohn*, *Jan Mazánek*, *Michael Kostrzewa*, *Wolfgang Schindler*, and *Rolf Steinberger*[*]

The special structural and steric properties of peptide-bound proline are investigated by use of definite linear and cyclic oligopeptides of proline and glycine and of proline alone. Their conventional and solid-phase synthesis is described mainly in relation to peculiarities and difficulties that arise from the conformation.

Conformation-dependent physical properties such as IR, UV, CD, and NMR spectra are investigated in detail for the free linear peptides and for those protected on the N and C ends, particularly with reference to criteria for the chain length required for helix formation and the influence of the end groups. The study of the solvent dependence of the configuration of the peptide group in oligoprolines led to the detection of *cis* linkages and to the isolation of *cis*-peptides with uniform configurations.

In the case of cyclic peptides particularly interesting points are the conformations of medium-sized rings with rigid arrangements of the amino acids, as in the cyclodipeptide c-Pro-Pro, the cyclotripeptide c-Pro-Pro-Pro, and the cyclotetrapeptide c-Pro-Gly-Pro-Gly, in comparison with the conformations of the more flexible cyclohexapeptides c-Pro-Pro-Gly-Pro-Pro-Gly and c-Pro-Gly-Gly-Pro-Gly-Gly and of the corresponding polymers, which are also ordered and relatively rigid.

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Energy and Entropy Parameters of Different Species of Carbanions from the Polymerization Kinetics and from Conductivity Measurements on Polystyryl-sodium in Polar Organic Solvents

By *M. Chmelíř*, *B. J. Schmitt*, and *G. V. Schulz*[*]

The anionic polymerization of vinyl monomers exhibits two kinetically unusual effects: 1, In solvents having different polarities, the polymerization rate varies by up to five orders of magnitude under otherwise identical conditions; 2, the temperature dependence of the propagation constant appears to be in total conflict with the Arrhenius equation.

The following model was proposed in 1965 for the solution of the resulting problems[1]. The carbanion end group exists in three well-defined forms (contact ion pair, solvent-separated ion pair, and free anion), which add monomer with rate constants that differ by orders of magnitude. The solvent and the temperature influence primarily the equilibria between these three species and hence the polymerization rate. Their direct influence on the rate constants does not go beyond that of the usual solvent effects.

Experimental and theoretical methods have been developed to determine the equilibrium and the rate constants for the three species as a function of the temperature from the polymerization kinetics[2] in various solvents. This gives the enthalpy and entropy differences between the species, as well as the dissociation constants and the Arrhenius parameters of their propagation constants. Conductivity measurements on "living" polymers in various solvents over a wide temperature range lead to dissociation constants that agree with those found kinetically. They prove the existence of the three types of the carbanion end group and allow the determination of the thermodynamic parameters of the corresponding equilibria.

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Synthesis of Polymer Gels with Covalently Incorporated Nucleoside Residues and Their Use for the Separation of Nucleic Acid Structural Units

By *H. Schott* (lecturer) and *Gerd Greber*[*]

Nucleoside derivatives with one or two methacryloyl substituents in the sugar residue were prepared by acylation of the nucleosides uridine, adenosine, cytidine, and guanosine with methacryloyl chloride. Free-radical copolymerization of these mono-unsaturated and di-unsaturated nucleoside derivatives gives crosslinked gels with covalently incorporated nucleoside residues, which swell both in water and in DMSO/$CHCl_3$(2:3). With the aid of these U, A, C, and G gels, it was possible to separate nucleoside mixtures and mixtures of nucleic acid structural components by the affinity chromatography principle, since the nucleic acid structural components interact specifically with the nucleoside residues fixed on the gel by base-pairing mechanisms. The importance of hydrogen bonds and of the stacking effect to the observed specific base pairings is discussed on the basis of the separation results.

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Diolefin Polyreaction in the Homogeneous Phase

By *Jürgen Hinz*, *Wolfgang Gebert*, and *Hansjörg Sinn* (lecturer)[*]

The reaction of butyllithium with isoprene in diethyl ether yields methyloctenyllithium compounds, which give 36% of 2-methyl-1-octene and the *cis-trans* isomers of 3-methyl-2-octene in the ratio 63:1.

On removal of the diethyl ether from the methyloctenyllithium by distillation after repeated addition of *n*-heptane, the hydrocarbons are found in a ratio of 26:74, whereas after renewed addition of diethyl ether, the ratio of 36:64 is found again.

The methyloctenyllithium compounds thus undergo reversible solvent-dependent rearrangement. Considerable 1,4 addition of isoprene to butyllithium also takes place in diethyl ether.

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Whereas the rate constants

$k_s = 1.6 \times 10^{-4}\,l\,mole^{-1}s^{-1}$ and $k_w = 1.5 \times 10^{-2}\,l\,mole^{-1}s^{-1}$

are found at -10 °C for the polyreaction of isoprene with butyllithium as the initiator, the corresponding values for the polyreaction of butadiene are

$k_s = 4.5 \times 10^{-5}\,l\,mole^{-1}s^{-1}$ and $k_w = 2.4 \times 10^{-3}\,l\,mole^{-1}s^{-1}$

The kinetically detectable association behavior of polyisoprenyllithium is described by

$K_3 = 1.86 \times 10^{-9}\,mole^2\,l^{-2}$

and

$K_6 = 2.80 \times 10^{-21}\,mole^5\,l^{-5}$

while the values for polybutadienyllithium are

$K_3 = 2.98 \times 10^{-9}\,mole^2\,l^{-2}$

and

$K_6 = 2.76 \times 10^{-20}\,mole^5\,l^{-5}$

The assumption that 1,4 linkage always occurs first, and that the product then isomerizes under the reaction of the initiator, is supported by the increase in the content of compounds having the 1,4-*cis* structure with decreasing initiator concentration:

Initiator concentration (mole/l)	1,4-*cis* structure	
	isoprene	butadiene
3×10^{-2}	80%	35%
5×10^{-5}	95%	70%
$< 10^{-5}$	98%	–

The rearrangement demonstrated resolves the conflict between the postulated primary step and the structure of the products obtained.

Investigations on Fragments of Phenylalanine-Specific tRNA

By *Rainer Thiebe*[*]

The transfer ribonucleic acids (tRNAs) constitute a group of relatively small molecules among the nucleic acids. Their molecular weights are in the region of 25000—30000, corresponding to chain lengths of 75—87 nucleotides.

In the course of protein biosynthesis, amino-acylated tRNAs are bonded to messenger RNA. The linkage of the amino acids to the tRNA is catalyzed by an enzyme. The tRNA is bonded to the messenger RNA by hydrogen bonds. The esterification is extremely specific; each tRNA can be coupled to only one of the 20 amino acids by the enzyme. Thus corresponding to the 20 amino acids, there are at least 20 tRNAs[1].

Some pure tRNAs have been isolated and sequenced. A number of rules can be deduced from a comparison of the primary structure of the tRNAs analyzed so far. These rules and some experimental observations point to a certain similarity in the tertiary structure.

The questions in which we are primarily interested are as follows: What is the reason for the high specificity with which the tRNA is recognized by the enzyme? Is this determined by the entire structure or only by a certain region? If it is a certain region, which?

A number of relatively large fragments of a tRNA have been prepared by chemical and enzymatic methods. Experiments have been carried out with individual isolated fragments and with combinations of fragments in an effort to answer the above questions. It was shown by omission or modification of various regions of the tRNA that a large part of the molecule is not necessary for the specific recognition by the enzyme[2].

A second set of problems is concerned with the steric structure of tRNAs. Whereas the final solution will probably be obtainable only by X-ray analysis, we have been able to contribute to the solution of a part of the problem by optical measurements on fragments. Experimental confirmation has been found in this way for the model of the secondary structure, which was originally based on theoretical considerations[3].

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[1] For a review, see *K. Miura*, Progr. Nucleic Acid Res. and Mol. Biol. *6*, 39 (1967).

[2] *R. Thiebe* and *H. G. Zachau*, European J. Biochem. *5*, 546 (1968); *P. Philippsen, R. Thiebe, W. Wintermeyer*, and *H. G. Zachau*, Biochem. Biophys. Res. Commun. *33*, 922 (1968); *R. Thiebe* and *H. G. Zachau*, *ibid. 36*, 1024 (1969); *K. Harbers*, Dissertation, Universität München 1970.

[3] *R. Römer, D. Riesner, G. Maass, W. Wintermeyer, R. Thiebe*, and *H. G. Zachau*, FEBS Lett. *5*, 15 (1969); *W. Wintermeyer, R. Thiebe, H. G. Zachau, D. Riesner, R. Römer*, and *G. Maass*, *ibid. 5*, 23 (1969).

Topochemical Polymerization of Monomers with Conjugated Triple Bonds

By *G. Wegner*[*]

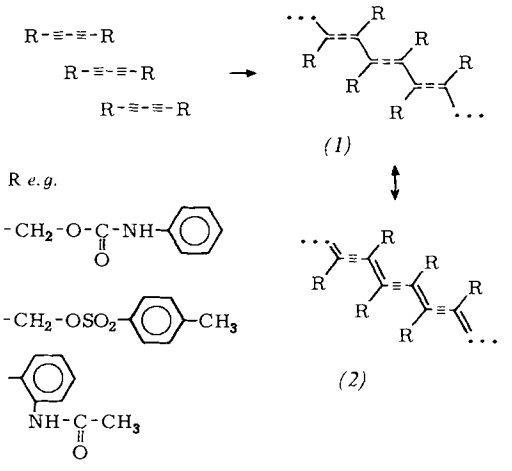
Many monomers containing two conjugated triple bonds polymerize in the crystalline state when heated to temperatures below their melting point or when exposed to visible or UV light to give deeply colored crystalline polymers.

Diacetylenes of this type with substituents that can form directional coordinate bonds are particularly reactive. Substituents of this nature favor a ladder-like arrangement of the monomer molecules in their crystal lattice. The rungs of the ladder are formed by the conjugated triple bonds, and the side-pieces with the aid of the coordinate bonds between the substituents. In such an arrangement, pairs of triple bonds of adjacent molecules approach to a distance of at least 3 Å from each other. The polymerization takes place along the ladder by successive tilting of each rung or by shearing of the entire ladder. Polymers with three cumulated double bonds per repeating unit and with a continuous conjugated main chain are formed from the conjugated triple bonds according to a 1,4 addition. On the basis of X-ray data, the main chain can be described either as a substituted poly-*trans*-butatriene *(1)* or as a mesomeric polybutenyne *(2)*.

Neither the shape nor the lattice of the monomer crystals generally changes in the topochemical polymerization of diacetylenes. Polymers with very high molecular weights can be obtained. The polymer crystals "as polymerized" exhibit strong dichroism with respect to the fiber axis (direction of strongest absorption) and are electrically

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conducting. The specific resistances are around $10^9-10^{13}\,\Omega$ cm ($E_a = \approx 0.8-1.0$ eV), depending on the substituents on the main chain.



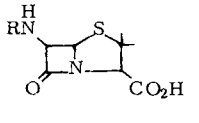
The reaction leading from monomers with conjugated triple bonds to linear high polymers can also be applied to crystallizable polymers with conjugated triple bonds in the repeat unit. It then acts as a topochemical crosslinking reaction.

German version: Angew. Chem. *83*, 366 (1971) [VB 268 IE]

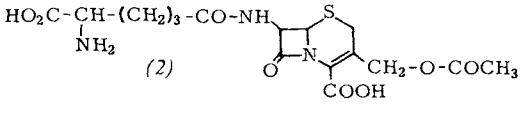
Recent Advances in Penicillin Chemistry

By *J. H. C. Nayler*[*]

The penicillins contain a common nucleus consisting of fused β-lactam and thiazolidine rings, with different acylamino side-chains at C-6. Benzylpenicillin (penicillin G) *(1a)* and phenoxymethylpenicillin (penicillin V) *(1b)* are still produced industrially by growing a Penicillium mold in the presence of phenylacetic acid and phenoxyacetic acid respectively, but the newer "semisynthetic" penicillins are prepared *via* the parent amine of the series, 6-aminopenicillanic acid (6 APA) *(1c)*. This substance was first isolated in 1957 from fermentations to which no side-chain precursor had been added, but it is now obtained more conveniently by removing the phenylacetyl side-chain from penicillin G *(1a)* with a bacterial enzyme. Simple chemical hydrolysis ruptures the β-lactam amide bond preferentially, but an ingenious procedure for directing the attack on the secondary amide function of the side-chain has been devised recently. A penicillin ester is treated under very mild conditions with phosphorus pentachloride followed by an alcohol, and very mild acid hydrolysis of the resulting imidate gives 6 APA *(1c)* and the alkyl phenylacetate.



(1a), R = $C_6H_5CH_2CO$
(1b), R = $C_6H_5OCH_2CO$
(1c), R = H



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Thousands of semi-synthetic penicillins have been prepared by acylation of 6 APA. Those derived from sterically hindered acids have the advantage of not being inactivated by the β-lactamases produced by many bacteria, and are particularly useful in treating staphylococcal infections. Valuable activity against Gram-negative bacteria is shown by α-aminobenzylpenicillin (ampicillin) and α-carboxybenzylpenicillin (carbenicillin). Their preparation involves temporary protection of the side-chain substituent, and the methods used are compared and contrasted with those employed in peptide synthesis.

In contrast to the many useful antibiotics produced by modifying the penicillin side-chain, modification of the nucleus usually reduces antibacterial activity. However, the cephalosporins represent a related group of β-lactam antibiotics in which a dihydrothiazine ring replaces the thiazolidine ring. Cephalosporins are prepared at present from cephalosporin C *(2)*, a metabolite of a Cephalosporium mold, by replacing the aminoadipyl side-chain with other acyl groups. Much attention is however being given to the chemical conversion of penicillins into cephalosporins, and this aspect of penicillin chemistry is likely to become increasingly important.

Lecture at Aachen, December 11, 1970 [VB 273 IE]
German version: Angew. Chem. *83*, 335 (1971)

Influence of Chlorine Attached to the Double Bond of Unsaturated Five-Membered Ring Carbonates and Anhydrides on Dienophilic Activity

By *Hans-Dieter Scharf, Werner Küsters*, and *Jörg Fleischhauer*[*]

The activation parameters of the dienophiles listed in the Table toward 9,10-dimethylanthracene have been determined.

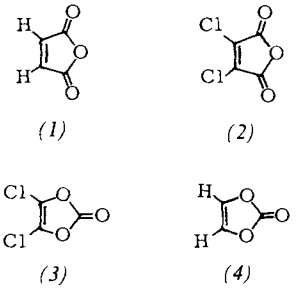


Table 1. Activation parameters of the Diels-Alder reactions of compounds *(1)*–*(4)* with 9,10-dimethylanthracene.

	Dienophile			
	(1)	*(2)*	*(3)*	*(4)*
$\tilde{\nu}$ (C=C) (cm^{-1})	1590 R [a]	1617 R [a] 1615 IR	1682 R [a]	1622 R [a]
Total bond order of C=C (EHT calculation)	1.18	1.15	1.32	1.34
$10^4\,k_2$ at 130 °C (l $mol^{-1}\,s^{-1}$)	14100	145	8.33	1.68
E_A (kcal mol^{-1})	10.9	13.3	17.6	26.1
$\Delta H^{\neq}$ (kcal mol^{-1})	10.2	12.6	16.7	25.0
$\Delta S^{\neq}$ (cal $mol^{-1}\,deg^{-1}$)	−33	−36	−32	−14.5
k_{rel} at 130 °C	8400	86	5	1

[a] R = Raman spectrum.

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In comparison with the values reported by *Sauer et al.*[1] for the reactivity of maleic anhydride *(1)* toward dienes, the dichloro derivative *(2)* is a distinctly poorer dienophile. However, in the case of the carbonates *(3)* and *(4)*, the dichloro derivative *(3)* exhibits a greater dienophile activity than the chlorine-free parent compound *(4)*.

The relatively positive entropy of activation of the reactions with vinyl carbonate compared to other compounds is worthy of note. Since no dependence of the rate constants on the solvent could be observed, it can be assumed that the molecule *(4)* requires a less ordered transition state than the usual dienophiles. Correlation of the activation energies E_A with the frequencies of the double bond in the IR or Raman spectrum or with the values for the total bond order determined by means of an EHT calculation with inclusion of the 3p electrons does not give linear relationships.

Lecture at Aachen on January 22, 1971 [VB 278 IE]
German version: Angew. Chem. *83*, 335 (1971)

[1] *J. Sauer, D. Lang,* and *A. Mielert,* Angew. Chem. *74*, 352 (1962); Angew. Chem. internat. Edit. *1*, 268 (1962); *J. Sauer, H. Wiest,* and *A. Mielert,* Chem. Ber. *97*, 3183 (1964).

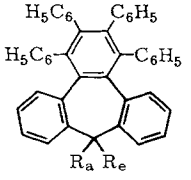
Stereochemical Investigation of Carbanion and Carbenoid Formation from Conformationally Rigid Cycloheptatriene Derivatives

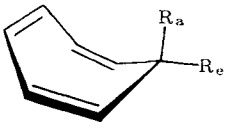
By *Werner Tochtermann*[*]

For 1,2,3,4-tetraphenyl-9*H*-tribenzo[*a,c,e*]cycloheptenes the boat conformation is "frozen" at room temperature ($\Delta G^{\neq} > 30$ kcal/mol for ring inversion of the seven-membered ring). Such compounds are thus suitable for a study of the reactivity of diastereotopic substituents on C-9 of the system and permit predictions about the relation between conformation and reactivity among benzologous cycloheptatrienes.

Remarkable differences of conformational origin were found in solvolytic experiments with conformational isomers of type *(1a)* and *(1b)*: only *(1b)* reacted readily with nucleophiles, and then with retention of conformation, *(1a)* being on the contrary relatively inert. On reaction with potassium *tert*-butoxide in [D_6]-dimethyl sulfoxide, tetraphenyltribenzocycloheptatriene *(2)* undergoes selective exchange of H_a for D, giving the monodeuterated hydrocarbon *(3b)*. The small amount of di- and tri-deuteration (determined mass-spectroscopically) permits the conclusion that the rate of exchange of H_e can be compared with that of the bridgehead hydrogens of triptycene; H_a, however, behaves similarly to the methylene-hydrogen atoms of diphenylmethane.

Reaction of the dichloro compound *(4)* with *n*-butyllithium at −100 °C apparently leads with high preference to the carbenoid *(5b)*, as shown by formation of *(6a)* on addition of deuterium oxide.





(1a), R_a = H; R_e = Cl
(1b), R_a = Cl; R_e = H
(2), R_a = H; R_e = H
(3b), R_a = D; R_e = H
(4), R_a = Cl; R_e = Cl

(5a), R_a = Cl; R_e = Li
(5b), R_a = Li; R_e = Cl
(6a), R_a = D; R_e = Cl
(7b), R_a = COOH; R_e = Cl

(5b), with its quasiaxial C—Li bond, couples with great rapidity, similarly to diphenylmethyllithium derivatives, with alkyl halides, *e.g.*, with added *n*-propyl bromide. With *(5a)*, however, one would expect rather a rapid coupling of *n*-butyllithium with the reactive quasiaxial C—Cl_a bond; such products could be detected only in small quantities by mass spectroscopy. Carboxylation of *(5b)* leads to the chloro carboxylic acid *(7b)*, whereas according to the literature[1] the conformationally mobile chloro(diphenyl)-methyllithium affords diphenylglycolic acid owing to hydrolysis of the C—Cl bond during working up. *(5b)* is also formed on metalation of *(1a)*.

A consideration of models reveals that the greater reactivity of R_a than of R_e may rest on stabilization of the transition state of the C—R_a cleavage by partial overlap with the π electrons of the neighboring benzene rings.

Lecture at Heidelberg (Germany) on January 12, 1971 [VB 279 IE]
German version: Angew. Chem. *83*, 336 (1971)

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[1] *D. F. Hoeg, D. I. Lusk,* and *A. L. Crumbliss,* J. Amer. Chem. Soc. *87*, 4147 (1965).

Steel embrittlement by hydrogen absorption has been studied by *C. D. Kim* and *B. E. Wilde* by electrochemical methods. To evaluate the steady-state surface concentration the adsorbed hydrogen is oxidized rapidly by an anodic pulse. With the aid of a membrane-permeation method the rate of hydrogen absorption into the iron lattice was measured: on one side of the membrane a steady-state hydrogen concentration is maintained, on the other side hydrogen is oxidized immediately. On an iron surface polarized cathodically in 10^{-4} M NaOH + 0.1 M Na_2SO_4 with current densities of 10—300 μA cm^{-2} surface coverages were 5—12% of a monolayer. The permeation method yielded a value of about 5 sec^{-1} for the hydrogen absorption rate constant in iron. The current densities used would effect corrosion rates of 0.1—4 mm/year. / J. Electrochem. Soc. *118*, 202 (1971) / –Hz.

[Rd 329 IE]

The kinetics of decomposition of aqueous perchloric acid at 295—322 °C in the concentration range often used in electrochemical work (1.1—6.6 mole/l) was studied by *M. P. Henderson, V. I. Miasek,* and *T. W. Swaddle*. The overall reaction is

$$2\,HClO_4 = H_2O + Cl_2 + 3.5\,O_2$$

Cl_2 is in equilibrium with $Cl^{\ominus}$ and HOCl. The initial reaction rate is to the power 3.5 of the perchloric acid concentration; the rate coefficient is $3.1 \cdot 10^{-7}$ $l^{2.5} mole^{-2.5} s^{-1}$ at 300 °C, and the overall activation energy 84 kcal $mole^{-1}$. The reaction is accelerated by its product $Cl^{\ominus}$ and decelerated modestly by $HSO_4^{\ominus}$. The reaction

$$2\,HClO_4 = H_2O + ClO_4 + ClO_3$$

is assumed to be the rate-determining step in the decomposition; ClO_4 and ClO_3 undergo fast reactions leading, finally, to Cl_2 and O_2. The chloride acceleration is thought to be due to the alternative reaction path

$$H^{\oplus} + HCl + ClO_4^{\ominus} = H_2O + Cl + ClO_3.$$

For application as an inert electrolyte the decomposition can be neglected for 1 M $HClO_4$ at 250 °C and for 0.2 M $HClO_4$ at 300 °C, if experiments of about a day's duration are involved. / Can. J. Chem. *49*, 317 (1971) / –Hz.

[Rd 330 IE]

The kinetics of disilane pyrolysis at initial pressures of 23 to 100 torr and 283—340 °C were investigated by *M. Bowrey* and *J. H. Purnell*. Product analysis by gas chromatography showed that initially only mono- and trisilane are formed. Secondary reactions also yield the isomeric tetrasilanes, solid $(SiH_2)_n$, and hydrogen. A detailed analysis of the experimental data excludes the occurrence of SiH_3 radicals as intermediates; the reactive species is silene SiH_2 (presumably in a bent singlet state). SiH_2 does not insert into Si—Si bonds nor into C—H or C—Si bonds, as was found by co-pyrolysis experiments with the methylated monosilanes. Insertion only takes place into Si—H bonds. Rate constants of these insertion reactions could be evaluated for several straight-chain, branched, and methylated silanes. They are practically independent of temperature. The enthalpy of formation of SiH_2 at 298 °K amounts to 247.5 kJ $mole^{-1}$. / Proc. Roy. Soc. *A 321*, 341 (1971) / –Hz.

[Rd 331 IE]

A new versatile method for the evaluation of electron affinities of molecules has been developed by *J. J. deCorpo* and *J. L. Franklin*. Both the appearance potential and the average translational energy of negative ions are measured in a mass spectrometer. The negative ions are formed by reactions of the type

$RX + e = X^- + R$ (dissociative electron attachment).

If the heats of formation of the reactants and products are known, (adiabatic) electron affinities can be calculated. The method was applied to the evaluation of the electron affinities of the halogen molecules formed by reactions of the type mentioned above starting with carbon tetrahalides. The values are in the range 2.5—2.9 eV; no trend can be recognized in the series from F_2 to I_2. / J. Chem. Phys. *54*, 1885 (1971) / –Hz.

[Rd 332 IE]

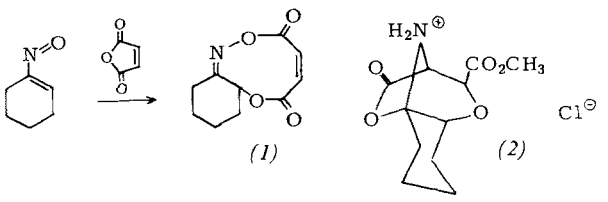
Hydrogen atoms in UV irradiated acid aqueous solutions of indole and 3-β-hydroxyethylindole were detected by *J. Feitelson via* scavenging with isopropanol: molecular hydrogen is formed and the hydroxyisopropyl radical disproportionates yielding isopropanol and acetone. It is known that the excited singlet state of indole releases solvated electrons into the solution, and that protons are effective quenchers of indole fluorescence. The pH dependence and the influence of oxygen on the yield of hydrogen atoms indicate that fluorescence quenching by protons is not effected by direct electron transfer from excited indole to H^+; the hydrogen atoms are formed by reaction of solvated electrons with protons. / Photochem. and Photobiol. *13*, 87 (1971) / –Hz.

[Rd 333 IE]

The molecular structure of gaseous chlorine isocyanate, ClNCO, has been determined by *H. Oberhammer* by electron diffraction. ClNCO was prepared by thermal depolymerization of trichloroisocyanuric acid. The scattering intensities could be interpreted equally well by two different structural models. One contains a linear NCO group, and the N—C and C—O distances differ widely from those found with similar molecules. The other model has an NCO group bent by about 10°, and the bond lengths are in the ranges expected. The rotational constants known from microwave spectroscopy solve the problem favoring the second model with the bond distances (in Å units) Cl—N 1.700 ± 0.002, N—C 1.227 ± 0.005, C—O 1.156 ± 0.006 and the angles ClNC 118.2 ± 0.6° and NCO 171.0 ± 2.1°. Semiempirical MO calculations also indicate a bent NCO group with the Cl atom in *trans* position to the O atom. / Z. Naturforsch. *26a*, 280 (1971) / –Hz.

[Rd 334 IE]

Reaction of nitrosocyclohexene with maleic anhydride leads, according to a report by *G. Just* and *W. Zehetner*, not to the expected Diels-Alder adduct but to the 1:1 adduct *(1)*. Nitrosocyclohexene is prepared by treating α-chlorocyclohexanone oxime with triethylamine in benzene at room temperature. On adding maleic anhydride the blue color disappears with formation of *(1)*, m. p. 205—208 °C (dec.). This 1:4 addition of anhydrides to nitrosoolefins seems to be of a general nature. With dimethyl acetylenedicarboxyl-

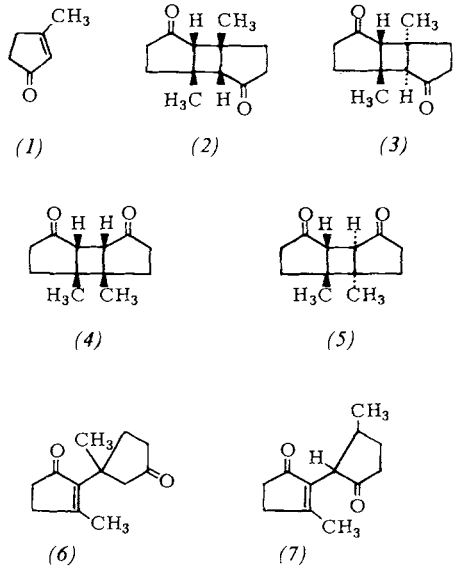


(1) (2)

ate or tetracyanoethylene, no identifiable product was obtained. On prolonged standing in presence of 0.5 N methanolic HCl, compound *(1)* undergoes a novel rearrangement quantitatively to give the salt *(2)*, m. p. 180 °C (dec.). / Chem. Commun. *1971*, 81 / –Ma.

[Rd 335 IE]

The photodimerization of 3-methyl-2-cyclopenten-1-one *(1)* (in benzene, 20 °C, Hg high-pressure vapor lamp, $1 > 300$ nm) has been investigated by *G. Mark, H. Matthäus, F. Mark, J. Leitich, D. Henneberg, G. Schomburg, F. v. Wilucki,* and *O. E. Polansky. (1)* is the first α,β-unsaturated cyclic ketone whose irradiation in solution affords all four possible *cis*-coupled cyclobutane isomers [compounds *(2)*—*(5)*]. Two dimers, *(6)* and *(7)*, having an oxocyclopentylcyclopentenone skeleton were also formed in the



(1) (2) (3)

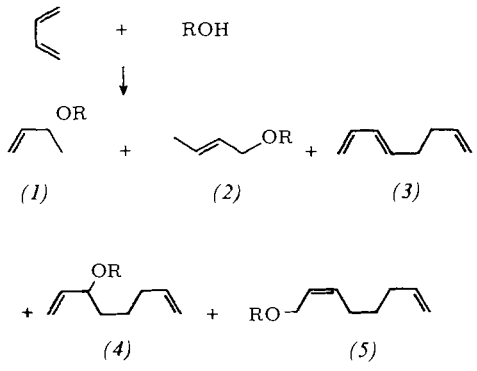
(4) (5)

(6) (7)

irradiation [*(2)*—*(7)*: 9.0 : 31.2 : 38.4 : < 0.5 : 20.3 : 0.9]. The ratio of dimers is dependent on solvent and concentration. / Monatsh. Chem. *102*, 37 (1971) / –Ma.

[Rd 336 IE]

The telomerization of butadiene with alcohols in the presence of nickel-complex catalysts to give 2,7-octadienyl ethers as main product is described by *T. C. Shields* and *W. E. Walker*. The nickel complexes, *e. g.* nickel pentanedionate, have to be used together with arylalkoxyphosphanes. Heating the nickel complex in presence of phenyldiisopropoxyphosphane, some $NaBH_4$ in O_2-free methanol, and butadiene to 100 °C in a pressure tube gave the following mixture: 3-methoxy-1-butene *(1a)*, 27.4%; 1-methoxy-2-butene *(2a)*, 6.7%; 1,3,7-octatriene *(3a)*, 17.8%; 3-methoxy-1,7-



(1) (2) (3)

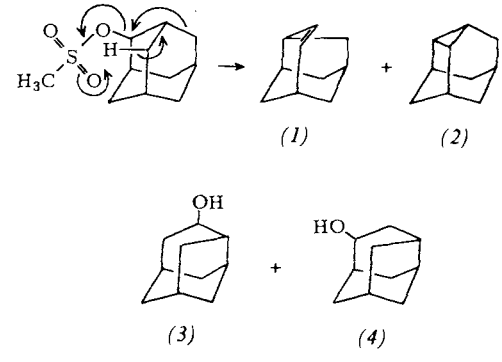
(4) (5)

(a), R = CH_3; *(b)*, R = C_2H_5; *(c)*, R = C_6H_5

octadiene *(5a)*, 31.3%. With ethanol, more octadienyl ether *(5b)* is formed. Isopropanol gave hydrocarbon oligomers and 1,5-cyclooctadiene as main product. With phenol and catalytic amounts of phenolate the main product is 1-phenoxy-2,7-octadiene *(5c)*. / Chem. Commun. *1971*, 193 / –Ma.

[Rd 337 IE]

Protoadamantene *(1)* **and 2,4-cycloadamantane** *(2)* are, according to a report by *J. Boyd* and *K. H. Overton*, readily obtainable by pyrolysis of 2-adamantyl methanesulfonate on Na_2CO_3-coated glass wool at 520 °C/0.5—0.7 torr helium. A 2 : 3 mixture of *(1)* and *(2)* is formed in yields of 90—95% (separation on $AgNO_3$—Al_2O_3). Hydroboration of *(1)* with B_2H_6 in THF at 25 °C gives the four isomeric



(1) (2)

(3) (4)

protoadamantanols *(3)* and *(4)* (with α- and β-OH), which on oxidation with RuO_2 and $NaIO_4$ afford the corresponding ketones. / Chem. Commun. *1971*, 211 / –Ma.

[Rd 338 IE]

Active Carbon. Manufacture, Properties and Applications. By *M. Smišek* and *S. Černý*. Elsevier Publishing Company, Amsterdam–London–New York 1970. 1st Edit., vii, 479 pp., *ca.* DM 97.—.

Active carbon has long been known in the form of carbo animalis, blood charcoal, *etc.*, but it was only at the beginning of this century that it was first manufactured on a commercial scale. It soon found a wide field of applications as an adsorbent and as a catalyst or catalyst support. Depending on the way in which it is produced, active carbon may have narrow or wide pores; the first type is better suited to the adsorption of gases or vapors, and the second to the adsorption of dissolved substances.

The present book is a revised and improved translation of a volume originally published in 1964 in Czech, in which other authors were involved in the writing of certain chapters. It deals with the manufacture and many of the applications of active carbon, and the theory of adsorption and the various equations for describing adsorption isotherms, together with methods for measuring the pore volume and the pore radius distribution, are all given in detail. However, the reader will seek in vain for *de Boer*'s recently developed t-method for the determination of pore size distribution. Although eight pages are devoted to the catalytic oxidation of hydrogen sulfide on active carbon, there is no mention of the process for the separation of sulfur dioxide from flue gases by means of active carbon.

The authors have taken some trouble to give as comprehensive a survey as possible of the current knowledge on active carbon. In a book of this size, however, details can only be handled very briefly. Because of its limited subject matter, the book will only be of use to a relatively small circle of specialists.

H. P. Boehm [NB 965 IE]

Chemie und Technologie der Silicone (Chemistry and Technology of Silicones). By *W. Noll*. Verlag Chemie, Weinheim 1968. 2nd Edit., xvi, 612 pp., 124 illustrations, 115 Tables, bound, DM 98.—.

The first edition appeared in 1960[1] and the present second edition in 1968. It is characteristic of the rapid overall growth in the chemistry and technology of macromolecular substances that after eight years this book, dealing with a specific field, required a fundamental revision, amplification, and extension; we should be thankful that this has in fact been done. This is particularly true of the chemistry of the low-molecular organosilicon compounds, the technology of silicone rubbers, and the copolymers obtained by various methods. The diligence and thoroughness with which the revision has been carried out can be seen by a comparison of the literature references, which are given at the end of each chapter and (in the new edition) listed on the contents page. Unfortunately, there is no author index to enable the work of a given author to be located.

The author is justified in pointing out in the foreword that the extension of Chapter 4 (present length *ca.* 50 pages, as opposed to 20 previously) on the chemistry of low-molecular organosilicon compounds, which have indeed been the starting-point for further developments, was particularly necessary. Here and in Chapter 7 (Copolymers) there are very informative tables.

The value of this book, which concentrates on essentials, can be seen by comparing Chapter 7 (Other Organosilicon Polymers, 42 pp.) with "Organosilicon Heteropolymers and Heterocompounds" (Plenum Press, New York, 1970, 568 pp.), the English translation of the monograph by *Borisov*, *Voronkov* and *Lukevits*, in which no summarizing survey is given.

For the many readers who are interested in polymeric organosiloxanes, Chapter 6 is still very important. This chapter gives a survey of the fundamentals of chemical and steric structure, the types of bonding, the effect of substituents, the Si—C bonding (comparison with C—C bonding), and the intermolecular forces. This survey leads to a better understanding of the overall properties and thus of the technical and operational behavior.

The very high standard of presentation of the book could be improved still further if certain important concepts (*e.g.* configuration, tacticity, conformation) were used consistently.

The book is strongly recommended to all those interested in the chemistry and technology of macromolecular substances.

Werner Kern [NB 960 IE]

Fortschritte der Verfahrenstechnik (Advances in Process Technology). Edited by *W. Springer*. Verlag Chemie, Weinheim 1969. 1st. Edit., xxvii, 1243 pp., 93 illustrations, 31 Tables, linen binding, DM 260.—.

The publication explosion in the field of chemical engineering continues, and it is becoming increasingly difficult to obtain an overall picture of progress in this branch of engineering. The annual publication of "Fortschritte der Verfahrenstechnik" is an attempt to meet this need, and now we have the eighth volume containing the literature for 1966–1967.

The very fact of the delay in publication (the first annual volume covered the period 1952–1953 and appeared as 1954) shows that the subject specialist cannot expect this type of compilation to act as a report on recent progress in his own particular field (computer-based SDI systems are far more suitable for this purpose) but rather to give him a survey of advances in subjects related to but different from his own. The individual sections of the latest volume fulfil this task with varying degrees of success. For example, the newly instituted Section 8, "Methods of Optimization", meets the above requirements and does it extremely well. On the other hand Section 7, "Technical Reactions and Reactors", still retains an arrangement which not only makes it difficult to get a comprehensive view of the topic, but also does not make use of the advances made in the systematics of this topic in the meantime (*e.g.* reaction analysis as opposed to reactor design).

If individual sections are omitted from time to time (*e.g.* in the present volume "Physics of High and Ultrahigh Pressures" and "Distillation and Rectification") in order to arrive at long-term critical evaluations rather than just a simple arranging and listing, then this is all to the

[1] Cf. Angew. Chem. *74*, 914 (1962).

good; Section 24, "Mechanical Separation of Liquids", which has reappeared in Volume 8, appears to the present reviewer to be a step in this direction.

The overall arrangement of the volume, with sections on Theory of Flow (Section 1), Rheology (Section 2), High-Pressure Technology (Section 3) *etc.* on the one hand and Flotation (Section 22), Mixing in the Viscous, Intrinsically Viscous, Multiphase, Paste, Powder, and Granular States (Section 26b), *etc.* on the other shows how difficult it is to achieve a logical division of the entire field. A search for research results in a specific topic will often necessitate reference to several sections of the book, and will often reveal the presence of duplicate entries.

The collection of over 11000 literature references has been assembled with much care. The note on abstracts of certain of the references in the "Verfahrenstechnische Berichte" is useful. Like its predecessors, this volume will help many chemists and engineers to gain a general picture of recent developments in the field of process technology; it is only a pity that the high ofice will prevent many from purchasing their personal copres

Hanns Hofmann [NB 959 IE]

The Chemistry of Indoles. Organic Chemistry, a Series of Monographs, Vol. 18. By *R.J. Sundberg*. Academic Press, New York–London 1970. 1st ed., x, 489 pp., £ 11.45.

The book provides a 500 page review of the advances made in indole chemistry between about 1950 and 1969, with reference to 1357 publications.

The author has made an excellent job of dividing up the great volume of subject matter and making the book readable and interesting. The main aspects of indole chemistry are presented in ten chapters containing many formulas and reaction schemes. The chapters deal with: 1. Electrophilic Substitutions on the Indole Ring; 2. General Reactions of Substituted Indoles; 3. Synthesis of the Indole Ring; 4. Synthesis of Special Indole Derivatives; 5. Oxidation, Degradation, and Metabolism of the Indole Ring; 6. Rearrangements, Ring Expansion, and Ring Opening Reactions of the Indoles; 7. Hydroxyindoles and their Derivatives; 8. Aminoindoles; 9. Ketones, Aldehydes, and Carboxylic Acids Derived from Indole; 10. Naturally Occurring Derivatives of Indole and the Indolines, and their Physiological and Medical Importance.

The first few chapters are divided according to mechanism, and an excellent idea of the reactivity of the indole ring is therefore gained from many examples. Where possible, the reactions found for indole are compared with those of other groups of substances. The presentation is assisted by a large number of tables.

The author places great value on the clarification of every reaction, and he is critical of any results that seem uncertain to him. Syntheses are placed in the forefront of the discussion.

It was obviously necessary to limit the discussion of indole alkaloids, their synthesis, and their biosynthesis. Preference has been given here to reactions that take place on the indole ring itself.

The author has succeeded in abstracting all the essentials from a subject matter that has now grown almost beyond comprehension.

The reviewer considers the book to be particularly successful, and recommends it to all chemists who are concerned with indoles, as well as to all libraries in the field. The book is essential to everyone whose work involves the synthesis of indoles.

Hans Plieninger [NB 956 IE]

Comprehensive Biochemistry. Edited by *M. Florkin* and *E. H. Stotz*. Vol. 18: Lipid Metabolism. Elsevier Publishing Company, Amsterdam-London-New York 1970. 1st edit., xv, 398 pp., numerous figures, bound Dfl. 75.—.

Lipids, once neglected by biochemists because of their complex behavior and analytical difficulties, are nowadays at the center of interest on account of their important role in the structure and function of biological membranes. Their metabolism is the preparatory stage for these physiological tasks. In animals this begins with resorption after the ingestion of food, mobilization of free fatty acids from the depots, and transport of the triglycerides in the plasma, leading *via* biosynthesis in the liver and other organs, especially nerve tissue, to breakdown by β-oxidation. In addition to this, bacteria and plants have their own individual lipid metabolism.

The chapters and compilations of this volume of "Comprehensive Biochemistry"[*], which roughly follow the scheme set down are once more written by competent authors practised in the art of writing surveys. The coordination of the chapters is somewhat careless, so that a number of repetitions and overlaps occur, and some authors use different nomenclature. However, the efforts made by the editors to obtain the necessary degree of cooperation from the authors should not be underestimated: an apologetic and reproachful note reveals that delays by a few of the authors—obviously overburdened by other literary duties—had a deleterious effect not only on the completion but also on the unity of the volume. This explains the gaps in the book, namely the lack of chapters on fat synthesis in higher organisms, fatty acid oxidation, steroid metabolism and end oxidation. The latter had already been moved from Vol. 17 to Vol. 18 for the same reason, and it is now intended to produce a special volume, which will not make the handbook, already expensive in itself, any cheaper. In the chapters offered, however, the metabolism of simple and complex lipids is very comprehensively, but critically covered and fairly selectively documented up to 1968. The length of the sections is not always in accordance with the biological importance of the material, but all contain a great deal of information so that the volume deserves a plade at the side of the others.

L. Jaenicke [NB 926 IE]

[*] Cf. Angew. Chem. internat. Edit. *8*, 995 (1969).

Chemistry through the Language Barrier. By *E. Emmett Reid*. Johns Hopkins Press, Baltimore–London 1970. 1st ed., xi, 138 pp., bound £4.75.

In this book, which has the subtitle "How to scan chemical articles in foreign languages with emphasis on Russian and Japanese", it is the author's aim to pass on his technique for reading information from foreign-language publications without learning the language. Since only 55.9% of all publications are written in English, the English-speaking chemist must encounter a large number of articles that are not in English.

The author builds up his method for the understanding of foreign-language publications, particularly the experimental part, from the assumptions that numbers, chemical formulas and equations, and names of compounds are the

same or similar in all languages and that in order to understand scientific articles it is more important to know the field of science than to be familiar with the language. The peculiarities of the following languages, collected in language groups, are described in a space of 64 pages: Italian, French, Romanian, Spanish, Portuguese (Romance group); Dutch, Swedish, Danish, Norwegian, German (Germanic group); Hungarian, Finnish, Czech, Polish, Russian (Slavic group); Japanese. Examples of texts are given for each language, with explanations. Special space is devoted to the introductions to the peculiarities of Russian and Japanese (presentation of the Russian alphabet, table of the Japanese Katakana and Hiragana [phonetic characters]). The 74 page Appendix consists of a multilingual vocabulary of the words of greatest importance to the chemist, and a list of Chinese characters used in Japanese texts for words such as acid, atom, to boil, *etc.* Despite the tips given by the author, it will not be easy to obtain information in this way, particularly since abstracting periodicals present the information in a more easily understandable manner, and there is a growing tendency for the journals to include English summaries of the articles. However, the book should be useful to the reader who is interested in languages.

Christian Weiske [NB 954 IE]

Physical Principles and Techniques of Protein Chemistry, Part A. From the Molecular Biology series. An International Series of Monographs and Textbooks. Edited by *S. J. Leach*, Academic Press, New York–London 1969. 1st Edit., xii, 530 pp., numerous figures, $ 24.00.

Some fifty years' research into proteins has resulted not only in an increase of knowledge of their structure and function, but also in an extension of the methods used for their study. In addition to chemical and biochemical methods, physical methods are being used with increasing success. Although in many cases only an expert can master them, some degree of familiarity with their physical foundations, their range of applications, and in particular with the interpretation of the results obtained is a necessity for any chemist working in the protein and peptide fields. Any new information source is desirable, and for this very reason this collection of papers under the editorship of *S. J. Leach* is to be welcomed.

The present volume (Part A) contains: 1. Electron microscopy of globular proteins *(E.M. Slayter)*; 2. X-Ray methods *(D.B. Fraser* and *T. P. MacRae)*; 3. UV absorption *(J.W. Donovan)*; 4. Fluorescence of proteins *(R. F. Chen, H. Edelhoch,* and *R. F. Steiner)*; 5. Perturbation and flow techniques *(B.H. Haysteen)*; 6. Dielectric relaxation *(S. Takashima)*; 7. Electrical birefringence and dichroism *(K. Yoshioka* and *H. Watanabe)*; 8. Electrophoresis *(R.J. Cann)*; 9. Analytical gel filtration *(D.J. Winzer)*.

Both the authors and the editor have succeeded in taking into account the current significance of the methods under discussion. Practical hints are given even for the methods used by non-specialists, and specific methods, where the greatest emphasis is on the range of applications, are carefully distinguished. The way in which the articles are distributed between the two volumes is somewhat less satisfactory; the present reviewer would have thought it more logical to collect related topics (*e.g.* spectroscopy) into one volume.

It will only be possible to estimate the importance of the book for scientific work when the second volume has appeared. In the meantime we can certainly say that a good and profitable book has been added to the "Molecular Biology" series.

Karel Bláha [NB 946 IE]

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New Routes to Multicomponent Oxide Glasses

By Helmut Dislich[*]

Multicomponent oxide glasses can be produced not only by melting methods but also by hydrolysis and condensation of alkoxide complexes with several metals. This requires temperatures only up to the transformation range of the glass in question, usually 500–600 °C. The process does not pass through the molten phase. It is possible to obtain glasses or polycrystalline substances, depending on the composition. The method is particularly suitable for the production of thin, transparent multicomponent oxide layers of almost any composition on substrates. Some of these layers provide protection against climatic attack or against oxidation.

1. Introduction

It is generally known, though rarely mentioned, that glass is the oldest thermoplastic. There is no reason to think of the materials and methods of organic chemistry in connection with glass, since the ASTM definition of glass is "an inorganic product of fusion, which has cooled to a solid state without crystallizing"[1].

The concept of the "vitreous state" will not be discussed here. The wisdom of including a production process (melting) in the definition seems questionable, since the definition then depends on the state of the art at the time of its formation. It results from the fact that for 4000 years, glass has been produced almost exclusively by melting, and from the technical importance that is attached to the further development of the melting process and of fused glasses. However, unfused glasses are also known. *Mackenzie*[2] has compiled an annotated list of unconventional routes leading to glass (Table 1).

The simplest method is hydrolysis; *Schroeder*[5] prepared vitreous layers of individual and mixed oxides (SiO_2, TiO_2, and others) by hydrolysis and polycondensation of metal alkoxides. However, single-oxide glasses are special cases, and if one wishes to carry out investigations and to obtain information about glass in general, the methods used must also be suitable for the preparation of complicated multicomponent glasses such as occur in industry.

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The first step in this direction was made by the use of at least one hydrolyzable metal compound in the preparation of a multicomponent glass; this allowed the use of a lower melting temperature[6]. *Roy*'s "gel method"[7] ultimately also aims in this direction. In this method, silica sols and metal carbonates, hydroxides, nitrates, *etc.* are combined to form gels, from which glasses are obtained below the liquidus temperature but above the transformation temperature. No details are known, but layers of multicomponent glasses will presumably not be obtainable in this way.

Table 1. Unconventional routes to glass (after [2]).

Glass production in solid state: (a) Shock-wave treatment (b) Neutron bombardment
Glass production from the vapor phase: (a) Direct methods, *e.g.* evaporation of crystalline Al_2O_3 and deposition of a noncrystalline Al_2O_3 film, recently also simultaneous evaporation of several individual oxides, which deposit as a glass film [3] (b) Indirect methods, *e.g.* vapor-phase hydrolysis of $SiCl_4$ to SiO_2. (c) Preparation of multicomponent glass films by the "Chemical Vapor Deposition" process [4].
Glass production from solution: (a) Oxide films produced anodically from aqueous electrolytes (b) Hydrolysis of *e.g.* metal alkoxides

Multicomponent glasses have not so far been obtained at temperatures not exceeding the transformation point. This seems a desirable achievement, for the following reasons.

1. It would no longer be possible to describe the glass structure merely as the structure of a supercooled melt, as has been common until now, since no temperature ranges in which crystallization occurs at a measurable rate are traversed during cooling. Since the properties of a glass are known to depend on its past history, glasses with novel "histories" would be available for investigation.

2. The axiom "glass is a product of fusion" would be replaced by *Mackenzie*'s definition[2]: "Glass is a noncrystalline solid", or by *Krebs*': "Glass in the wider sense can be defined as a solid with dense packing of the atoms, in which crystalline arrangements do not extend beyond a few interatomic distances".

3. Preparation below the transformation temperature would provide at least a possibility of obtaining glasses that cannot be obtained at higher temperatures because of an excessively strong tendency to crystallize.

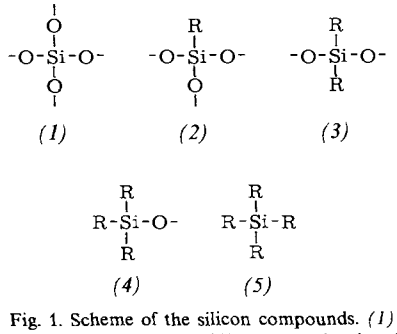
Since hydrolytic methods are well suited to the production of layers, it would be possible to apply coatings of multicomponent glasses to substrates that are stable up to the transformation temperature of the glass to be applied. This is only very rarely possible by other methods.

Nothing much can be said at present about points 1 and 3. Points 2 and 4 are in the forefront at present, and particularly the route by which multicomponent oxide glasses and also crystalline multicomponent oxides can be prepared. This is where organic chemistry plays its part, for it provides this route. There is much here that is old, insofar as the starting materials are hydrolyzable metal compounds, particularly metal alkoxides, which can be readily degraded to the metal oxide. The novelty is the advantage that is taken of the strong tendency of alkoxides of various elements to react *with one another*. These reactions lead to "alkoxo salts", which are often very complicated, and which are then degraded by hydrolysis and polycondensation to multicomponent oxide glasses and crystalline multicomponent oxides.

2. Position and Statement of Problem

Let me first recall the old silicate-silicone comparison (the contents of the following lines are based on *W. Noll*'s book[8]).

The smaller the number of organic residues R in Figure 1, the more pronounced is the silicate character of the corresponding polymers; the type *(1)*, which is the only one



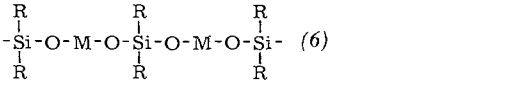
(1) *(2)* *(3)* *(4)* *(5)*

Fig. 1. Scheme of the silicon compounds. *(1)*: Structural unit of the silicate network; *(2)—(4)*: structural units of the silicone polymers; *(5)*: "pure" organosilicon compound.

with which we shall be concerned, must be regarded as a structural unit of an "inorganic polymer".

The search for heat-resistant plastics led to attempts to use the principle of the Si—O framework of the silicates, but instead of the tetrafunctional group *(1)*, which leads to highly crosslinked products, the groups *(2)–(4)*, whose functionality can be read off directly, were incorporated. The resulting successes of silicone chemistry are well known.

On the whole, attempts to extend the structural principles of silicate chemistry farther into organosilicon chemistry by transition to heteroorganopolysiloxanes *e.g.* of the type *(6)*[*] (M = *e.g.* B, Al, Ti, Sn, Pb, P, As[8]) have so far been technically less successful. The investigations, which are



(6)

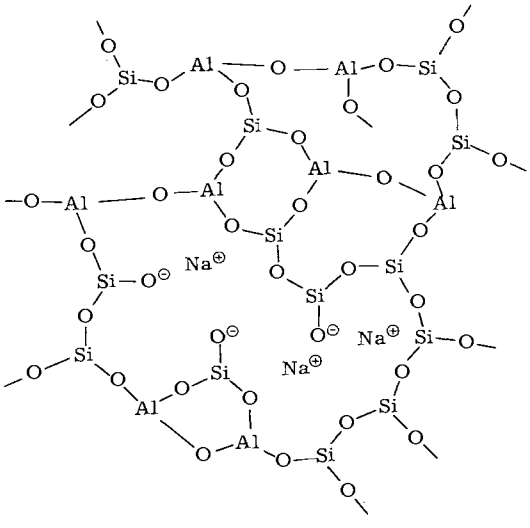


Fig. 2. Section of the structure of a multicomponent glass. Silicon forms a fourth bond to oxygen in the third dimension.

intended to yield polymers that can be processed at low temperatures, have not yet been completed. Such polymers are not highly crosslinked; the functionality of the monomers is limited by the incorporation of groups R. Polymers of this type often have more or less irregular compositions, and this makes the "starting material/end product" correlation very difficult[9].

Silicate glasses are highly crosslinked, but are nevertheless thermoplastics. Their thermoplasticity, unlike that of organic polymers, is due to the rupture of principal valences in the network as a result of thermal motion at high processing temperatures. The structural groups in silicate glasses correspond to type *(1)* above in the case of silicon, and to the analogous type having the highest functionality in the case of the other metals. Figure 2 shows a section from the structure of a multicomponent glass containing some of these groups.

The simplest case is silica glass, which can be prepared[5] from esters of silicic acid by hydrolysis and polycondensation, formally in accordance with

[*] Shown with bivalent M for simplicity.

$$Si(OR)_4 + 4\ H_2O \longrightarrow [Si(OH)_4] + 4\ ROH$$

$$[Si(OH)_4] \xrightarrow{-2\ H_2O} SiO_2$$

though the reaction undoubtedly proceeds *via* polyorganoxysiloxanes, and not *via* $Si(OH)_4$.

In the practical application of this "structural unit principle" for the production of multicomponent glasses and crystalline multicomponent oxides, the metal alkoxides provide a good source of monomeric structural units with maximum functionality. The maximum functionality is a necessary (but not sufficient) condition, since all the organic groups must be split off to obtain pure oxide systems. This is trivial in the case of a single metal alkoxide. When many metal alkoxides are present together, the following questions are of interest:

1. Can a multicomponent glass be prepared by the hydrolysis and polycondensation methods commonly used in organosilicon chemistry *without going through the molten phase*?

2. Can crystalline multicomponent oxides be prepared in the same way from the reactive metal alkoxides?

The first efforts were concerned with known multicomponent glasses and crystalline multicomponent oxides. This has the advantage over the heteroorganopolysiloxanes *(6)* that the end products can also be obtained by another route, *e.g.* by melting, and it is therefore possible to compare the properties of the products obtained by the known method and by the new route.

3. Some Known Reactions of Metal Alkoxides

Metal alkoxides have been known for a long time, and have been studied intensively and systematically during the last twenty years, particularly by *Bradley*[10,11] and *Mehrotra*[12], who cite hundreds of original articles in their reviews[10-12]. Reference should also be made to[13].

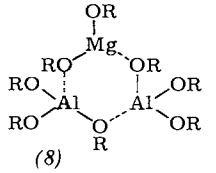
These reactions of the metal alkoxides are particularly important to the following discussion:

1. Many metal alkoxides react readily with one another to form complex metal alkoxides, the "alkoxo salts". The stability of these salts increases with the difference in the electrochemical characters of the two metals. The complexes may be heteropolar, *e.g. (7)*, or homopolar, *e.g. (8)*.

$$Al(OR)_3 + KOR \longrightarrow [Al(OR)_4]K$$

(7)

$$2\ Al(OR)_3 + Mg(OR)_2 \longrightarrow$$



(8)

2. All metal alkoxides can be more or less readily hydrolyzed, as illustrated earlier for $Si(OR)_4$.

3. During the hydrolysis, condensation reactions take place with formation of polyorganoxymetaloxanes, some of which are polymeric, *e.g. (9)* and *(10)*.

$$M(OR)_x + H_2O \rightarrow M(OH)(OR)_{x-1} + ROH \quad (9)$$

$$M(OH)(OR)_{x-1} + M(OR)_x \rightarrow (RO)_{x-1}MOM(OR)_{x-1} + ROH \quad (10)$$

$$2\,M(OH(OR)_{x-1} \rightarrow (RO)_{x-1}MOM(OR)_{x-1} + H_2O \quad (10)$$

The end product of the hydrolysis, after elimination of water from OH groups by heating, is the metal oxide, which may be regarded as a macromolecule built up from three-dimensionally linked metaloxane chains —M—O—M—O—.

Other reactions that sometimes complicate the situation, but do not fundamentally change it, can be indicated briefly by some typical examples (Fig. 3).

$$>B\text{-}OH + RO\text{-}Si\lessdot \longrightarrow >B\text{-}O\text{-}Si\lessdot + ROH$$

$$>B\text{-}OH + HO\text{-}Si\lessdot \longrightarrow >B\text{-}O\text{-}Si\lessdot + H_2O$$

$$>Al\text{-}OR + HO\text{-}Si\lessdot \longrightarrow >Al\text{-}O\text{-}Si\lessdot + ROH$$

$$\geqslant Ti\text{-}OR + HO\text{-}Si\lessdot \longrightarrow \geqslant Ti\text{-}O\text{-}Si\lessdot + ROH$$

$$\geqslant Si\text{-}OR + HO\text{-}P(=O)\lessdot \longrightarrow \geqslant Si\text{-}O\text{-}P(=O)\lessdot + ROH$$

$$\geqslant Si\text{-}OR + R^1OH \longrightarrow \geqslant Si\text{-}OR^1 + ROH$$

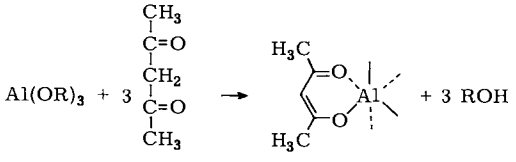


Fig. 3. Examples of crosslinking by metaloxane formation.

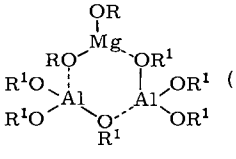
4. Preparation of Crystalline Multicomponent Oxides

Though we are interested mainly in glasses, we shall first consider the crystalline multicomponent oxides, since the reaction is much more straightforward, particularly in the case of spinel, which has only two components. The preparations are carried out in a temperature range in which the above reactions take place, *i.e.* up to about 500 °C. Reactions that take place in the melt, *i.e.* at much higher temperatures, do not occur.

4.1. Preparation of Magnesium-Aluminum Spinel

Magnesium methoxide is allowed to react with aluminum *sec*-butoxide in a molar ratio of 1:2 in alcohol. The magnesium aluminum alkoxide *(11)* is formed in solution [eq. (1)][13].

$$Mg(OR)_2 + 2\ Al(OR^1)_3 \longrightarrow$$



(1)

(11), $R = CH_3$, $R^1 = CH(CH_3)_2$

The choice of the organic residues is a matter of purely practical importance, since they are removed later in any case.

On evaporation of the solvent in the presence of atmospheric moisture, hydrolysis occurs [eq. (2)].

$$Mg[Al(OR)(OR^1)_3]_2 + 8\,H_2O \rightarrow \underset{(11)}{} \; Mg[Al(OH)_4]_2 + 2\,ROH + 2\,R^1OH \quad (2)$$

The resulting lumps of gel are then heated to 620 °C to induce the condensation, which undoubtedly also takes place in part even at room temperature [eq. (3)].

$$Mg[Al(OH)_4]_2 \rightarrow Mg[AlO_2]_2 + 4\,H_2O \quad (3)$$

4.2. Identification of the Magnesium-Aluminum Spinel

The small, hard, white lumps obtained were identified by X-ray diffraction analysis as spinel (crystallite size 100 Å). The principal reflections of spinel appear (though they are very broad) on heating at 250 °C, and become more pronounced on heating at 400 °C. The lattice constant at 20 °C is 8.084 Å (literature value 8.080 Å).

The product prepared by the alkoxide method at 620 °C absorbs water from the air on prolonged standing; this water can be rapidly removed by reheating to 620 °C. A product heated to 1150 °C no longer exhibits this water absorption. The X-ray diffraction diagram also becomes sharper. The crystallite size is then about 950 Å. The polycrystalline material contains MgO and Al_2O_3 in a ratio of 1:1.08.

The spinel is thus formed at temperatures far below those normally used for such syntheses. Whereas Mg and Al alkoxides react with one another even at room temperature, high temperatures are necessary for the normal reaction of salts or oxides. We allowed $Mg(NO_3)_2 \cdot 6\,H_2O$ to react with $NH_4Al(SO_4)_2 \cdot 12\,H_2O$, and found that spinel formation started only above 850 °C. According to *Hüttig et al.*[14], the formation of the zinc-aluminum spinel also begins at 850 °C, while the material consists entirely of spinel only at 1150 °C.

Bratton[15] uses lower temperatures. $Al(OH)_3$ and $Mg(OH)_2$ are precipitated together at 100 °C. Spinel is formed when the precipitate is heated at 350–400 °C (Fig. 4).

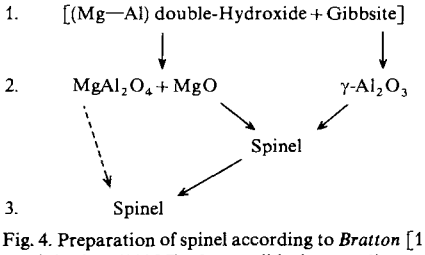


Fig. 4. Preparation of spinel according to *Bratton* [15]. 1: Simultaneous precipitation (100 °C); 2: possible intermediate stage (350—400 °C); 3: crystallization of spinel (> 400 °C).

The route *via* the alkoxides seems more direct; no crystalline phases other than spinel are formed even at low temperatures.

Hard, glass-clear spinel layers can also be applied to substrates by the method described in Section 7 (dipping method).

5. Scope of the Method

The formation of the spinel evidently depends on the prior reaction of the components in accordance with eq. (1), so that a sort of cocondensation occurs after hydrolysis instead of homocondensation. The latter possibility, which appears, from literature data, to be more common[16], would yield mixtures of single oxides instead of a homogeneous multicomponent oxide. Part of the metal alkoxides may naturally undergo condensation reactions with elimination of alcohol even at room temperature, but this is of no importance to the final result, since the reaction continues *via* the polyorganoxymetaloxane stage *(11)*. The temperatures mentioned are evidently necessary for the removal of the last traces of water from hydroxyl groups bonded to metal.

The process should be applicable to other elements if the metal alkoxides react with one another, as they do in most cases. For example, we have prepared eucryptite [LiAl(SiO$_4$)] in this way from lithium ethoxide, aluminum *sec*-butoxide, and $Si(OR)_4$. After this work had been concluded *Mazdiyasni, Dollof,* and *Smith*[17] reported the preparation of $BaTiO_3$, $SrTiO_3$, and $SrZrO_3$ as polycrystalline material by a similar method; this underlines the scope of the method. (Investigations on a similar basis are also being carried out at the ETH Zürich[18].)

This therefore provides a relatively convenient route to multicomponent oxides that are difficult or perhaps almost impossible to obtain by other methods, and also offers the possibility of obtaining substances of high purity. Very pure metals may be used in the preparation of the metal alkoxides, the alkoxides themselves or their reaction products may be recrystallized, and even distilled in some cases, and the reactions proceed under comparatively mild conditions, so that contamination from the walls of the vessel can be avoided. The method may also be of value for doping.

Finally, there is practically no other method that allows the preparation of thin layers of multicomponent oxides having almost any desired composition on substrates (see Section 7). The method is particularly elegant for this purpose, since the action of atmospheric moisture (hydrolysis) and the removal of the condensation products water and alcohol can be achieved without difficulty in the case of thin layers (a few tenths of a μm). The preparative difficulties in the production of polycrystalline material are sometimes considerable, since the diffusion paths are long and difficult to control, unlike those in thin layers. This can lead, with rising temperatures, to pyrolysis with separation of carbon before the hydrolytic removal of the OR groups is complete. Though this does not interfere with the necessary determination of the nature of the material obtained, the product is not obtained in the pure state. However, an improvement can generally be achieved by the use of different experimental conditions, often established only by laborious trial and error.

5.1. Preparation of Borosilicate Glass

Unlike the organic polymers, which are versatile in spite of restriction to a few elements, the inorganic polymers, *i.e.* the glasses, owe their versatility to the fact that their composition can include practically any element from the periodic system.

To prepare a multicomponent glass, the various components must be made to react with one another. In the melting method, favorable conditions are provided by heating the starting materials until they melt; the various components then react with one another, possibly with elimination of gases such as CO_2. The melt may then, for example, be poured into a mold, where it cools and solidifies to form a glass.

Since a multicomponent glass containing silica can be regarded, on the basis of its structure (Fig. 2), as a crosslinked "polymultimetaloxanesiloxane", it seemed interesting to us to look for a practical route that would also justify this description. As in the spinel case, metal alkoxides should combine here to form an alkoxo complex, which is converted by hydrolysis and polycondensation *via* "polyorganoxymultimetaloxanesiloxanes" into the glass, which contains no organoxy groups, and is in fact the "polymultimetaloxanesiloxane".

To provide a better grasp, an example of a practical procedure will now be described. A three-neck flask is fitted with a stirrer and a reflux condenser, and the following ingredients are introduced in succession with stirring, nitrogen being passed over the mixture at the same time: 50 g of ethanol (dry) + 0.5 g of 2,4-pentanedione; 102 g of $Si(OCH_3)_4$, 5.3 g of $Al(O\text{-}sec\text{-}C_4H_9)_3$, 10.5 g of $NaOCH_3$ (solution in methanol corresponding to 172 g of Na_2O/l), and 1.4 g of KOC_2H_5 (solution in methanol corresponding to 218 g of K_2O/l). The precipitate formed on addition of the aluminum *sec*-butoxide is brought into solution by stirring and heating at 70 °C. 11.2 g of H_3BO_3 dissolved in 120 ml of boiling ethanol is then added. The precipitate that forms dissolves within 5 minutes. The dark yellow solution contains about 160 g of oxides (80.9% SiO_2, 12.7% B_2O_3, 3.6% Na_2O, 2.2% Al_2O_3, 0.6% K_2O) per liter.

The diluted solution containing 30 g of oxide/l is left open to the air in a beaker. It sets to form a gelatinous mass, which is then heated for 9 hours at 150 °C. During this heating, it cracks and breaks up into small yellow crumbs, which become colorless, glass-clear, and hard when heated at 530 °C. Small black impurities that sometimes form (see above) are sorted out. This preparation route is illustrated in Figure 5.

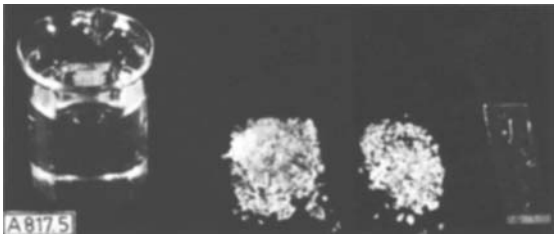


Fig. 5. Preparation of a borosilicate glass from hydrolyzed alkoxides. From left to right: starting solution, crumbs obtained by hydrolysis at 20 °C, crumbs obtained from these by heating at 550 °C, glass obtained from these on pressing at 2800 atm.

5.2. Proof that the Product is a Borosilicate Glass

Though the presence of clear, transparent fragments allows little doubt as to the nature of the product, the properties of a product prepared in this way must be compared with those of a fused glass in order to provide rigorous proof that a glass has in fact been formed in the region of the transformation temperature, without fusion. A portion of the glass-clear crumbs was therefore pressed into transparent plates at 630 °C and 100 t (this can be achieved more easily at 650–700 °C), and another portion was fused at 1600 °C. The investigations described below were carried out on the crumbs, the molded plates, and the fused pieces, and show that glass has in fact been formed (see Table 2).

Table 2. Chemical composition of the borosilicate glass (values in wt.-%).

Glass	SiO_2 (%)	B_2O_3 (%)	Al_2O_3 (%)	Na_2O (%)	K_2O (%)
Unfused	86.85	5.91	2.62	3.92	0.66
Fused	87.99	4.97	2.62	3.67	0.67

The reason for the greatly reduced B_2O_3 content in comparison with that in the original solution is that part of the B_2O_3 escapes as esters of boric acid. It should be remembered that 10–15% of the B_2O_3 used in the melting method can also escape with the flue gases.

The residual water content can be determined by IR spectroscopy (OH band at 2.9 μm).

Unfused glass contains 0.036% of H_2O after a fragment has been heated for 50 h at 550 °C and pressed at 650 °C. If the same glass is heated for 4 h at 700 °C under a high vacuum before pressing, 0.029% of water can still be detected. Fused glass contains 0.023% of H_2O (for comparison, Duran 50, which is fused on a large scale, contains 0.033% of H_2O).

The water is thus very extensively removed during the normal condensation at 550 °C (followed by heating for a short time at 650 °C during pressing).

The residual carbon content of an unfused glass is 0.0002%, which is surprisingly low in view of the fact that the glass was made from alkoxides. The hydrolysis is thus practically quantitative, despite the strong crosslinking.

The hydrolysis resistance of unfused glass in accordance with DIN 12111 is 0.007 mg of Na_2O/g of coarsely ground glass (= hydrolytic class 1), while that of fused glass is 0.005 mg of Na_2O/g of coarsely ground glass (= hydrolytic class 1). Physical and optical properties are shown in Table 3.

The temperature function of viscosity was tested qualitatively by heating a fragment under constant load and observing it with the aid of a microscope. Deformation begins at 675 °C. The temperature function of viscosity corresponds to that of similar borosilicate glasses.

The agreement of the properties shows that the product does not consist of single oxides or a number of two-component oxides, but of a homogeneous multicomponent system, *i.e.* a borosilicate glass.

Let us now briefly compare the procedure for the hydrolytic condensation with that for the melting process. The batch is replaced by a mixture of compounds that react readily with one another. Homogenization is replaced by

dissolution in a common solvent. The reaction, which starts only at high temperatures in the melting process, begins here at room temperature (complex formation) and continues with the action of atmospheric moisture with hydrolytic elimination of alcohol, which is comparable to the thermal elimination of CO_2 from a carbonate. The condensation reaction with elimination of water takes place at the same time; this reaction requires temperatures up to the transformation range of the glass. The pouring of a fused glass into a mold is replaced by pressing of the glass crumbs to form a transparent molding in the transformation range.

Table 3. Physical and optical properties of the unfused and of the fused glass.

Glass	Density D_{20} (g/cm³)	Coefficient of expansion	Transformation temperature (°C)	Hardness to scratching
Unfused	2.28	32×10^{-7}	590	scratches window glass and apparatus glass 20
Fused	2.27	32×10^{-7}	610	scratches window glass and apparatus glass 20

Glass	Refractive index n_d 20	ν_d	X-ray diffraction analysis
Unfused	1.477	65	contains no crystalline phases
Fused	1.474	66	contains no crystalline phases

This last step is obviously more difficult than a melting process. Moreover, because of the simultaneous reaction of five components, it is not so easy to explain the path as in the case of the two-component system of spinel. Since the initial and final states are known with certainty, we could write a formal reaction equation, but we shall not do so here. A first glimpse is provided by following the IR spectrum of a film of borosilicate glass 0.5 μm thick on a barium fluoride plate during its formation. After 30 min at 100 °C, a pronounced metal-OH band is observed at 3 μm, which is stronger after 30 min at 250 °C. After 30 min at 530 °C, the metal-OH groups have been consumed by condensation, and can no longer be detected, at least in this thin layer. A band at 3.4 μm is attributable to the CH_3 and/or CH_2 vibration of the OR residues that have not yet been removed (or of the free alcohol). It is present after heating at 100 °C, but has disappeared at 250 °C, when hydrolysis has progressed to an advanced state. The boric acid band is situated at 7.2 μm and the Si—O vibration at 9.4 μm. The characteristic of the curve corresponds to that of a Duran 50 film (though the boric acid content of the latter is considerably higher) and to that of a vapor-deposited layer of borosilicate glass.

6. Conclusions

According to all the observations reported, a multicomponent oxide glass can no longer be regarded exclusively as an "inorganic product of fusion" (ASTM definition), but can also be considered with equal right as a "multipolycondensation product" prepared by hydrolysis and polycondensation reactions from compounds containing metal-OC groupings. Neither of these features is fundamentally essential or necessary to the definition. It is important and interesting, however, that practically no difference can be detected between a fused and a condensed glass by the investigation methods used. It may be possible, by more refined methods, to find differences due to the past history of the material, which could lead to further knowledge about glasses.

An important point as far as the method is concerned is that it is now possible to prepare a glass "from below", *i.e.* by approaching the glass state from a lower temperature. It is therefore no longer necessary to pass through the temperature range of maximum crystallization rate. With this release from the danger of crystallization during cooling, it should now be possible to establish whether a given composition that can be prepared by this method forms a glass or a crystalline phase. The method may also be of use in the study of phase separation phenomena.

7. Multicomponent Glass Layers on Substrates

It has only recently become possible to apply thin multicomponent glass layers to substrates by simultaneous vapor deposition of individual oxides under vacuum[3]. A particularly important step is the development of special "vapor deposition glasses", with which homogeneous glass layers suitable for technical use can be produced directly[19]. Glass layers can also be applied by the chemical vapor deposition process[4].

The process described can be used if the substrate does not soften below the transformation temperature of the glass to be applied. This is the simplest and above all the most versatile method, since it allows the application of coatings of multicomponent oxide layers having practically any desired composition[20]. The methods by which substrates with relatively large surfaces can be coated with oxide layers by dipping in organic solutions have been described in detail by *Schroeder*[21]. In analogy with these methods, we dipped the substrates to be coated (metal, glass, *etc.*) in the solution, removed it uniformly, and heated it for a short time at a temperature not exceeding the transformation range of the layer-forming glass. Solid, hard glass layers up to a few thousand Ångströms thick are obtained.

The layer formation itself takes place effortlessly. This is because the films are so thin that the diffusion of the water required for hydrolysis and of the eliminated hydrolysis products is greatly facilitated. For this reason we prepared many multicomponent glasses in thin layers after the formation of a glass had been proved for the borosilicate glass.

Examples are provided by experiments with solutions that lead to the following glass compositions: borosilicate glass layers (composition as described in Section 5.2), phosphate silicate glass layers (containing SiO_2, Al_2O_3, P_2O_5, BaO, B_2O_3, CaO, MgO), lead silicate glass layers (containing SiO_2, PbO, Na_2O), and alkali metal aluminosilicate glass layers (containing SiO_2, Na_2O, Al_2O_3).

All these layers are transparent, hard, and amorphous to X rays[22].

Even these few examples show the scope of the process. A limitation exists with respect to the thickness of the layers. Though some increase is possible by means of additives in the solution or by multiple coating, it is difficult to obtain layers more than 0.5 μm thick; this is no problem in the vapor deposition method. However, even thin layers have technically useful properties. Thus metals can be electrically insulated with multiple borosilicate glass layers. The same layers also prevent or inhibit the scaling of metals, *e.g.* of iron. Thus a coated sheet of iron shows no scaling when heated for 3 hours at 800°C, whereas an uncoated sheet of iron is completely scaled under such severe conditions. The tarnishing of brass *e.g.* at 530°C is also prevented, as is its corrosion. First experiments[23] indicate that in the salt spray test and in the condensation water test, white rust formation or corrosion begins only after 1600 hours, and is then spontaneous. A series of sensitive optical glasses can be very effectively protected against climatic attack by phosphate silicate glass layers (Fig. 6). This is important, since the concentration on certain optical properties in such glasses sometimes necessarily leads to poor stability to climatic conditions. It is also important here that the protective layers should be very thin, as they may otherwise affect the optical properties.

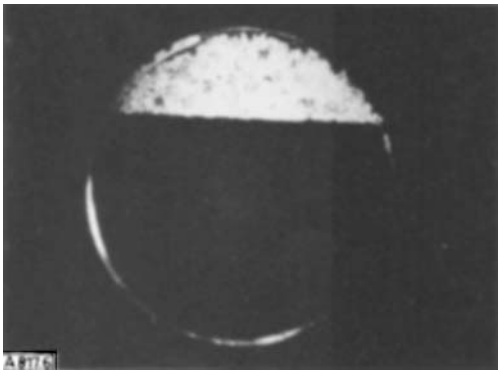


Fig. 6. Protection of an optical glass against climatic attack by coating with phosphate silicate glass. Top: uncoated (corrosion), bottom (coated).

8. Preparation of Starting Glasses for Glass-Ceramics

Glass-ceramics contain finely dispersed crystalline phases in a glass matrix. They are prepared by fusion of a starting glass containing nucleating agents. A controllable partial crystallization is then brought about by heat treatment. Probably the best-known property of some glass-ceramics of this type is their almost vanishingly small coefficient of thermal expansion of $0 \pm 1 \times 10^{-7}/°C$[24].

Starting glasses for glass-ceramics have also been obtained by the route described here. A solution of the alkoxides is first prepared such that the composition, converted to the oxides, corresponds to a Schott glass ceramic (61.4% SiO_2, 21.6% Al_2O_3, 6.8% P_2O_5, 3.8% Li_2O, 1.4% MgO, 0.5% Na_2O, 2.6% TiO_2, 1.9% ZrO_2[25]). This solution, with a total oxide content of 77 g/l, is used to prepare hard, transparent layers by dipping and heating (580°C, 30 min).

Attempts to convert this material into granular material by heating at 620°C yields transparent crumbs together with a few black components. The clear crumbs contain no crystalline material. These crumbs are treated further at 680°C and 830°C, in accordance with the temperature program for the completely analogous glass-ceramic starting glass prepared from the melt. This gives h-quartz solid solutions and nucleation phases containing ZrO_2. The crystallization properties correspond to those of the fused starting glass.

Another starting glass is prepared from a solution having the following composition (converted to oxides): 62.00% SiO_2, 21.86% Al_2O_3, 6.16% ZnO, 2.82% Li_2O, 1.77% TiO_2, 1.77% ZrO_2, 1.61% BaO, 1.11% MgO, 0.50% CaO, 0.40% K_2O[26]. A second solution has the same composition, except that it does not contain the nucleating agents TiO_2 and ZrO_2. It seems interesting to compare the products obtained from the two solutions. Clear layers can be prepared from both solutions; however, the crumbs obtained from both solutions are black. Differential thermal analysis gives a crystallization signal for the substance containing the nucleating agents, and none for the substance with no nucleating agent; this corresponds to the behavior of the fused starting glass.

I am grateful to my assistant of many years' standing, P. Hinz, who carried out all the preparations. I have been greatly assisted in the identification of the reaction products by many colleagues at the Jenaer Glaswerke Schott u. Gen., Mainz, by discussions and investigations. These, together with their assistants, were Dr. Coenen, Dr. Dörr, Dr. Dutz, Dr. Geffcken, Jenemann, Kristen, Lindig, Dr. Mulfinger, Dr. Neuroth, Dr. Petzold, Scheidler and Prof. Schröder. I am very grateful to Dr. Warnach and Ing. Steinhoff for carrying out the difficult pressing experiments.

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Nutmeg as a Narcotic

A Contribution to the Chemistry and Pharmacology of Nutmeg *(Myristica fragrans)*

By Dieter Abbo Kalbhen[*]

The abuse of nutmeg for narcotic purposes has led to renewed chemical and pharmacological interest in this drug. Several allylbenzene derivatives whose biological transformation products have structures resembling mescaline and amphetamine have been identified as psychotropic constituents. It is suggested that the intensity of the hallucinogenic action of these compounds is due to the possibility of simulation of LSD-like structural elements.

1. Introduction

Nutmeg has a very checkered history as a medicine. Though it was used in India and in the Arab countries as a spice and as a remedy as early as the year 700 BC, this drug was unknown to the Greeks and Romans, and it was only in the Middle Ages that it was introduced into Europe by Arab merchants and later by Portuguese and Dutch traders. The product, which came from the Moluccas in the East Indies, was the monopoly of the Portuguese and Dutch for a long time. It was not until 1843 that the British and French managed to break this monopoly by growing nutmeg trees on the islands of the Caribbean. Thus nutmegs are now available both from the East Indies and from the West Indies.

Like many other cooking spices, such as cloves, pepper, paprika, caraway, fennel, and aniseed, nutmeg was very important to the ancient Indians and Arabs as a medicine, and it is still found in the folk medicine of these countries. Various nutmeg preparations were and are used as analgesics, stomachics, digestives, hypnotics, aphrodisiacs, and amenorrheal agents. The European physicians of the Middle Ages, who borrowed many recipes and treatments from their Arab colleagues, prescribed nutmeg for an equally wide range of indications.

Whereas the use of nutmeg as a spice has persisted to the present day, its interest and importance in medicine has declined in Europe since the beginning of the 18th century. The end of the 19th century saw a brief return to popularity in the wake of a rumor that nutmeg is an effective abortifacient. Several medical journals at this period reported a high incidence of nutmeg poisoning in women.

Intoxication due to the benumbing and psychotropic effects of nutmeg had been described even earlier. Thus the famous Breslau physiologist *Purkinje*[1] carried out an experiment on himself; the symptoms that he described as resulting from the ingestion of three ground nutmegs are very similar to the effects of hashish. The excessive use of nutmeg in folk medicine as a stomachic, as an abortifacient, or in love potions leads in man to intoxication symptoms that are manifested in outbreaks of sweat, desire to urinate, headaches, nausea, disequilibrium, hysterical laughter, hallucinations, and/or stupor.

Though the hallucinogenic action was described repeatedly around the turn of the century, it was only after the second world war that nutmeg came to be used as a narcotic, and this use was mainly, if not exclusively, confined to the USA. This drug is used particularly by young people, students, hippies, and convicts to attain an intoxicated state with hallucinations. Since nutmeg is generally known as a spice, can be bought anywhere, and has even been used in prison kitchens, it is readily obtainable by the groups mentioned above, and is welcomed by them as a substitute for control-

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led substances such as marihuana, mescaline, and LSD. (The American government has now stopped the use of nutmeg spices in the kitchens of penal establishments.)

2. Constituents and Active Ingredients of Nutmeg

The wide availability and use of nutmeg as a spice and also its psychotropic and toxic effects aroused interest in the composition of this drug some time ago. A detailed analysis was reported by *Power* and *Salway* in 1907 and 1908[2, 3]. These authors showed by various extraction and distillation methods that nutmeg contains 25–40% of fatty oils (nutmeg butter), 8–15% of volatile oils, and 45–60% of structural materials containing cellulose.

The fatty oils from nutmeg have found little interest in medicine, and therapeutic uses have been concentrated mainly on the volatile oil. Thus the German Pharmacopeia valid until the end of 1968 and the Supplement, 6th edition, contained the nutmeg preparations listed in Table 1. The 7th edition of the German Pharmacopeia, which has been valid since January 1, 1969, no longer contains nutmeg and its preparations.

Table 1. Nutmeg preparations listed in the 6th Edition of the German Pharmacopeia (DAB VI) and the relevant supplement (Suppl. VI).

Oleum nucistae, oleum myristicae, nutmeg butter, DAB VI; oleum myristicae aethericum, oleum macidis, oil of nutmeg, DAB VI (also as a constituent of spiritus melissae compositus, DAB VI)
Semen myristicae, nutmeg kernel, Suppl. VI
Mace, Suppl. VI
Nutmeg butter, Suppl. IV

The components listed in Table 2 have been detected qualitatively and quantitatively in the further analytical investigation of the volatile oil of nutmeg, in which excellent results have recently been obtained, in particular by the use of gas-chromatographic methods.

Myristicin *(1)*, elemicin *(2)*, and safrole *(3)* have been identified as constituting the greater part (about 80%) of the group of allylbenzene derivatives.

Table 2. Constituents of the volatile oil of nutmeg.

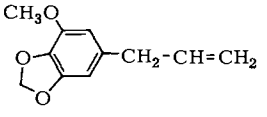
1) Terpene hydrocarbons	
α-pinene	toluene
β-pinene	*p*-cymene
camphene	linalool
sabinene	geranyl acetate
p-mentha-1,4-diene	cineol
p-mentha-1,4(8)-diene	camphor
p-mentha-1,8-diene	citronellol
p-menth-1-en-4-ol (4-terpinol)	citronellal
p-menth-1-en-8-ol	(+)-borneol
2) Allylbenzene derivatives [a]	
myristicin *(1)*	methylisoeugenol *(6)*
elemicin *(2)*	isoeugenol *(7)*
safrole *(3)*	isoelemicin *(8)*
methyleugenol *(4)*	methoxyeugenol *(9)*
eugenol *(5)*	
3) Myristic acid	
4) Unidentified substances	

[a] See Section 3 for formulas.

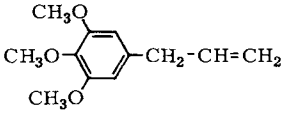
In the search for the medicinally active constituents, it was found that the nuts no longer had any action after the removal of the volatile oil. It was therefore concluded that the volatile oil, and particularly the main constituent myristicin, should be regarded as the active principle. Though *Warburg*[4] questioned the contribution of the volatile oils to the action of nutmeg in 1897, evidence obtained at the beginning of this century indicated that myristicin is responsible for the pharmacological and toxic effects of nutmeg oil[3, 5, 6].

3. Hallucinogenic Ingredients of Nutmeg

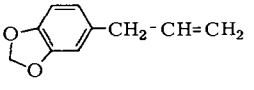
Following repeated confirmation by further investigations that the volatile oils are the principal cause of the effects of nutmeg, later work has been concentrated mainly on the allylbenzene derivatives *(1)*–*(9)* (see Table 2).



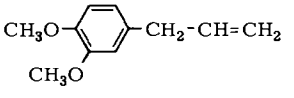
(1), Myristicin



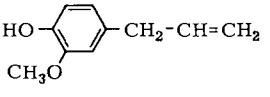
(2), Elemicin



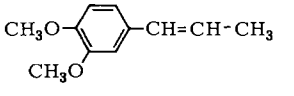
(3), Safrole



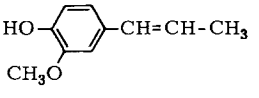
(4), Methyleugenol



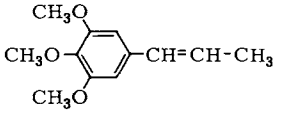
(5), Eugenol



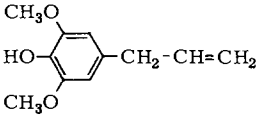
(6), Methylisoeugenol



(7), Isoeugenol



(8), Isoelemicin



(9), Methoxyeugenol

Of these allylbenzene derivatives, which are present in the volatile oil in quantities that vary with the region in which the nutmeg was grown, only myristicin *(1)* has so far been investigated pharmacologically as a single substance. Slight inhibition of monoamine oxidase occurred in mice, and a distinct psychotomimetic effect (see Section 4) has been detected in man. It should be mentioned in this connection, however that the action was always stronger when the other constituents of the volatile oil were administered at the same time. It is assumed that the terpene hydrocarbons do not themselves contribute to the psychotropic action, but promote the absorption of the allylbenzene derivatives by irritating the gastrointestinal tract.

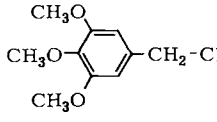
4. Hallucinogenic Action Pattern in Man

The use of nutmeg as a narcotic became known to large numbers, particularly of young people, through the autobiography of racial conflict victim *Malcolm X*[7], which has been widely circulated in the USA. Nutmeg preparations have been taken by many people as a substitute for cannabis, mescaline, or LSD, with the result that considerable knowledge now exists concerning the action pattern in nutmeg poisoning.

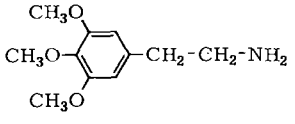
The drug is generally ground, stirred into a drink, and taken in a quantity of 5 to 30 g. The psychotomimetic action, which may range from a slight change in consciousness to very intense hallucinations, begins to take effect 2 to 5 hours after ingestion. Whereas visual hallucinations are less common than in LSD or mescaline intoxication, distinct changes are found in the perception of time and space. A feeling of soaring and of dissociation of the limbs from the body is frequently also reported. The main side effects noted are nausea, headaches, dry mouth, increased pulse rate, and giddy feeling. All the symptoms of nutmeg intoxication usually disappear after 12 to 48 hours. An occasional after-effect is a lasting aversion to the taste and/or smell of nutmeg. For this reason nutmeg is generally used only once or twice, very rarely more often, as a narcotic.

5. Biotransformation of the Allylbenzene Derivatives

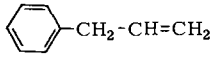
Shulgin has developed an interesting hypothesis to explain the hallucinogenic action of the allylbenzene derivatives[8]. Comparison of the structural formula of elemicin *(2)* with that of mescaline *(10)* shows a certain similarity. *Shulgin*[8] assumes that elemicin *(2)*, myristicin *(1)*, and the other allylbenzene derivatives are transformed into the amino derivative in the human body by direct transamination or by oxidation and subsequent transamination. As was discovered by *Kawabata*[9], the metabolism of allylbenzene



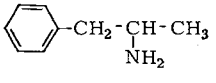
(2), Elemicin



(10), Mescaline

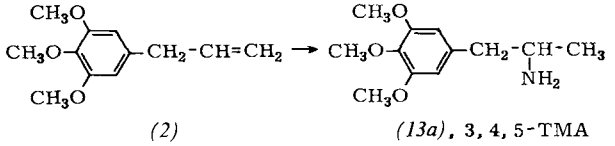


(11)

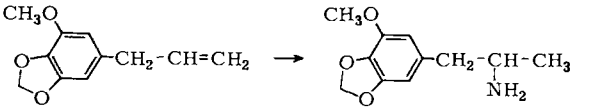


(12), Amphetamine

(11) leads to cinnamic acid, β-hydroxy-β-phenylpropionic acid, and *p*-hydroxyphenylacetic acid. *Barfknecht*[10] later found that allylbenzene fed to rats is partly also converted into amphetamine *(12)*. It therefore seems reasonable to assume the formation of 3,4,5-trimethoxyamphetamine *(13a)* from elemicin *(2)* and the formation of 3-methoxy-4,5-methylenedioxyamphetamine *(14a)* from myristicin *(1)*.



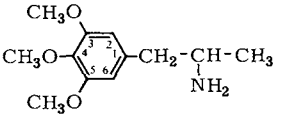
(2) *(13a)*, 3, 4, 5-TMA



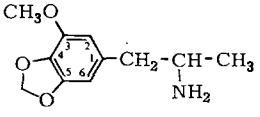
(1) *(14a)*, 3-M-4, 5-MDA

As can be seen from the formula of 3,4,5-trimethoxyamphetamine *(13a)*, it contains structural elements of amphetamine *(12)* and of mescaline *(10)*. The compound *(13a)*, which was synthesized in 1947 by *Hey*[11], exhibited twice the hallucinogenetic activity of mescaline in pharmacological tests. It is interesting to note that the stimulatory action component of amphetamine, which is manifested in increased blood pressure, increased pulse rate, and insomnia, is no longer present in the trimethoxy derivative *(13a)*. *Shulgin*[12] has recently synthesized other isomers of trimethoxyamphetamine and examined them for hallucinogenic action (Table 3).

Table 3. Relative hallucinogenic activities of the isomeric trimethoxyamphetamines (TMA) *(13)* and methoxymethylene-dioxyamphetamines (MMDA) *(14)* [activity of mescaline *(10)* = 1].



(13a)



(14a)

Isomer of *(13)*	Posn. of CH_3O	relative activity
a	3,4,5	2
b	2,3,4	0
c	2,3,5	< 7
d	2,3,6	< 10
e	2,4,5	17
f	2,4,6	12

Isomer of *(14)*	Position of CH_3O	Position of $-O-CH_2-O-$	relative activity
a	3	4,5	2
b	2	4,5	21
c	2	3,4	18

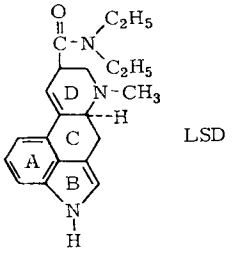
Besides the trimethoxy compounds, *Shulgin*[12] also synthesized and investigated substances in which two methoxy groups were replaced by a methylenedioxy group, *i.e.* isomers of *(14a)* (Table 3).

3-Methoxy-4,5-methylenedioxyamphetamine *(14a)* thus corresponds to the metabolite that should be formed in the body from myristicin *(1)* by transamination. The other allylbenzene derivatives in the volatile oil of the nutmeg could also be converted into the corresponding amphetamine derivatives by biotransformation. Detailed studies on the biotransformation of these allylbenzene derivatives are being carried out at present in animal experiments by *Kalbhen* and *Braun*[13].

6. Explanation of the Hallucinogenic Action of the Amphetamine Derivatives

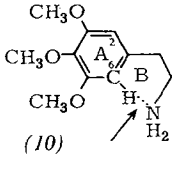
Pronounced quantitative differences are found in a comparison of the hallucinogenic effects of the isomeric trimethoxyamphetamines *(13)*. Since it could be shown that these substances are degraded and excreted by the body at the same rate and by the same metabolic pathway, and that the partition coefficients (between fat and water) of the isomers do not differ greatly, other explanations were sought for the difference in their hallucinogenic activities. *Snyder* and *Richelson*[14] have developed a hypothesis that allows an interesting explanation of this phenomenon.

Lysergic acid diethylamide (LSD) is well known to be by far the most potent of the hallucinogenic drugs discovered so far; even in a dose of 50—100 µg in man, it causes very intense hallucinations of long duration. On the basis of this intense action, the above authors assume that the LSD structure possesses optimum characteristics for the production of hallucinogenic effects. Its outstanding structural features are the indole skeleton and the two fused six-membered rings. For greater clarity in the following discussion, the rings have been labeled A, B, C, and D.

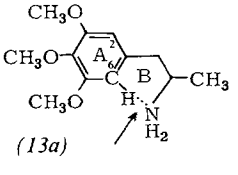


LSD

A comparison of the structures of hallucinogenic drugs containing no indole grouping with the structure of LSD shows that *e.g.* mescaline *(10)* and the amphetamine derivatives *(13)* and *(14)*, either formed by the metabolism of myristicin and elemicin or synthesized, have only the benzene ring A in common with LSD. In the case of mescaline, it is quite possible to simulate an indole structure by a change in the conformation of the side chain. This conformation can be stabilized by a hydrogen bond. The extent to which this intramolecular hydrogen bonding occurs naturally depends on the magnitude of the negative charge on C-2 or C-6, and this is determined in turn by the nature of neighboring substituents on the benzene ring. Because of the neighboring trimethoxy groups, the negative charge in mescaline is in fact greatest on C-2 or C-6; in this case, therefore, a sort of ring B can be formed, and hence an indole structure simulated, by intramolecular hydrogen bonding.



(10)

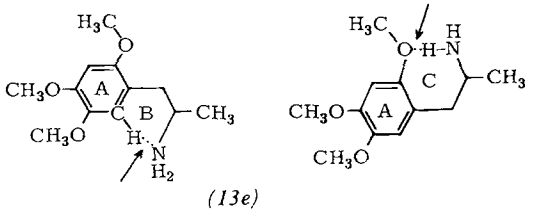


(13a)

It is interesting to observe that no hallucinogenic action could be detected for 2,3,4-trimethoxyamphetamine *(13b)*, in which hydrogen bonds of this nature cannot be formed.

Examination of the possibility of intramolecular hydrogen bond formation for the structures of the six isomeric trimethoxyamphetamines *(13)* yields interesting clues that contribute to the explanation of the difference in activity.

(13a) can form the ring B, and hence simulate the indole structure by hydrogen bonding in the same manner as mescaline *(10)*. This is also possible in *(13e)*. The latter substance can also form a hydrogen bond from the amino hydrogen to the oxygen of the 2-methoxy group, and the resulting structure approximates to ring C in the LSD molecule.



(13e)

It thus seems possible that 2,4,5-TMA *(13e)* can simulate rings B and C of LSD, though a molecule can naturally exist in only one of the two conformations at any given time.

The formation of ring C also depends on the freedom of movement of the methoxy group on C-2. An adjacent methoxy group, *i.e.* in position 3, hinders the free rotation of the methoxy group on C-2, with the result that ring C cannot be simulated. This would explain why the 2,3,5-trimethoxy derivative *(13c)* has a weaker hallucinogenic action than the 2,4,5-trimethoxy derivative *(13e)*, and why the 2,3,4-trimethoxy derivative *(13b)* is practically inactive.

The assumption that adjacent methoxy groups hinder the formation of a ring C conformation is confirmed by the investigation of compounds of the methoxy(methylenedioxy)amphetamine type *(14)*. Whereas *(13b)* is inactive and cannot simulate either ring B or ring C, 2-methoxy-3,4-methylenedioxyamphetamine *(14c)* has a strong hallucinogenic action, which can be attributed to the possibility of formation of a ring C conformation.

[1] *J. E. Purkinje*, Neue Breslauer Sammlungen aus dem Gebiet der Heilkunde *1*, 423 (1829).

[2] *F. B. Power* and *A. W. Salway*, J. Chem. Soc. *91*, 2037 (1907).

[3] *F. B. Power* and *A. W. Salway*, J. Chem. Soc. *93*, 1653 (1908).

[4] *O. Warburg*: Die Muskatnuss. Leipzig 1897.

[5] *A. R. Cushny*, Proc. Roy. Soc. Med. *1908-I*, 39; *H. H. Dale*, *ibid. 23*, 69 (1909); *F. Jurns*: On Myristicin and Some Closely Related Substances. Reports published by Schimmel & Comp., Leipzig 1904.

[6] *G. B. Wallace*: Contributions to Medical Research. Vaughn, Ann Arbor, Michigan 1903, p. 351.

[7] *Malcolm X* with *A. Haley*: The Autobiography of Malcolm X. Grove Press, New York 1964.

[8] *A. T. Shulgin*, Nature *210*, 380 (1966).

[9] *H. Kawabata*, Yakugaku Zasshi (J. Pharmac. Soc. Japan) *65*, 9 (1945).

[10] *C. F. Barfknecht*, cited by *A. T. Shulgin et al.* in *D. H. Efron*: Ethnopharmacologic Search for Psychoactive Drugs. Public Health Service Publication No. 1645, Washington 1967, p. 210.

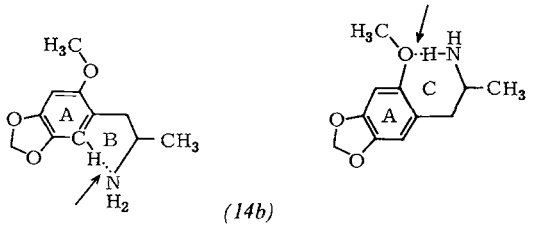
[11] *P. Hey*, Quart. J. Pharm. Pharmacol. *20*, 129 (1947).

[12] *A. T. Shulgin*, Nature *197*, 379 (1963).

[13] *D. A. Kalbhen* and *U. Braun*, to be published.

[14] *S. H. Snyder* and *E. Richelson* in *D. H. Efron*: Psychopharmacology. Public Health Service Publication No. 1836, Washington 1968, p. 1199.

2-Methoxy-4,5-methylenedioxyamphetamine *(14b)* can also simulate ring C and/or ring B, whereas 3-methoxy-4,5-methylenedioxyamphetamine *(14a)* can assume only a ring B conformation, as is also confirmed by the lower activity of the latter.



(14b)

On examination of the formulas of 2,3-dimethoxy-4,5-methylenedioxyamphetamine and 2,5-dimethoxy-3,4-methylenedioxyamphetamine, it can be predicted on the basis of the above working hypothesis that the second compound will have a stronger action than the first. This has been confirmed by pharmacological tests.

Finally, mention should also be made of 2,5-dimethoxy-4-methylamphetamine (DOM), which has become very popular in the USA as a psychodelic drug under the name STP. The very intense psychotomimetic action of this substance can be explained by the favorable position of the methoxy groups, which allow a ring B or/and ring C conformation. The methyl group on C-4 prevents rapid enzymatic degradation of this compound, and this may help to potentiate the action.

7. Closing Remarks

Though no specific receptor localizations and points of attack on the molecular level have been established as yet for LSD and the other hallucinogenic drugs described here, the above working hypothesis developed by *Snyder* and *Richelson*[14] offers a valuable contribution to the elucidation of the mode of action of these psychotomimetics. The abuse of nutmeg as a narcotic drug has given fresh impetus to pharmacological research in the testing of psychotropically active components, and this research has led through structure-action relations to a model possessing unquestionable interest. However, nutmeg is now almost without significance in practical medicine, and there is little likelihood, in view of its strong taste, that this well-known spice will remain popular for long as a narcotic drug.

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Bis(trimethylsilyl)diimine: Preparation, Structure, and Reactivity[1]

By Nils Wiberg[*]

Based on investigations carried out in collaboration with Wan-Chul Joo, Gerhard Schwenk, Wilfried Uhlenbrock, and Michael Veith

Dedicated to my father, Professor Egon Wiberg, on the occasion of his 70th birthday

The highly reactive compound bis(trimethylsilyl)diimine (BSD), which was first prepared by oxidation of lithium tris(trimethylsilyl)hydrazide, is light blue, sensitive to thermolysis and hydrolysis, and ignites spontaneously in air. On the basis of electron transfer, acid-base, or free-radical reactions, it acts in particular as a (preparatively useful) redox system and as an agent for the introduction of azo groups. Redox reactions lead by oxidation or reduction of the other reactant through two oxidation stages to hydrazine derivatives or molecular nitrogen, and in the case of electrochemical reduction, to BSD radical-anions. Azo-group transfers, on the other hand, yield new inorganic azo compounds with no change in the oxidation state of the diimine group.

1. Introduction

When we succeeded, in 1968, in synthesizing *bis*(trimethylsilyl)*diimine*[2]

$(CH_3)_3Si—N=N—Si(CH_3)_3$
BSD

as the first diimine completely substituted with silyl groups[3], the unexpectedly long-wave light absorption and the resulting radiant blue color of the compound immediately aroused our particular interest. The investigation of this substance, which has lost none of its original fascination, has proved worth while; it has revealed a varied, unusual, and interesting chemistry.

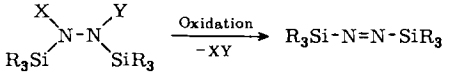
Various investigators had attempted to prepare a bis(silyl)diimine. The ability of carbon to form azo compounds *(1)*, which are often surprisingly stable (for

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example, azobenzene is stable up to 600 °C[4], makes the synthesis of "azosilanes" *(2)* a challenge in view of

$\geqslant C-N=N-C \leqslant$ *(1)* $\geqslant Si-N=N-Si \leqslant$ *(2)*

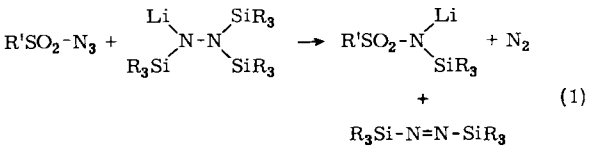
the group relationship between carbon and silicon. A possible preparation method was seen in the oxidation of 1,2-bis(silyl)hydrazines *(3)*.



(3) *(4)*

However, several attempts to verify this reaction[5-7] were initially unsuccessful because of failure to find an oxidizing agent that could oxidize bis(silyl)hydrazines *(3)* only to the stage of the readily oxidizable bis(silyl)-diimines *(4)* without oxidizing these further to nitrogen[8]. By the action of *p*-toluenesulfonyl azide on lithium tris-(trimethylsilyl)hydrazide (X = Li, Y = SiR_3 in *(3)*), we were able to obtain BSD as a readily sublimable product that crystallizes in the form of needles and melts at −3 °C[3].

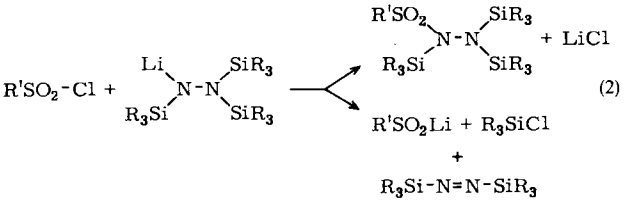
Including BSD and a bis(boryl)diimine that is obtainable from it[10], there are now ten classes of isolable diimine derivatives X—N=N—X (counting diimine itself) in which ligands X are linked to the azo group *via* main-group elements having various atomic numbers:



(1)

The arenesulfonyl azide, as in its reactions with CH-acidic methylene derivatives[18], evidently adds first to the silylhydrazide to form a nitrogen chain compound $R'SO_2—N=N—\overset{\ominus}{N}—N(SiR_3)—N(SiR_3)_2$, which can decompose after migration of silyl groups to give the final reaction products.

Instead of arenesulfonyl azides, arenesulfonyl chlorides may be used as the oxidizing agents[19]. In this case, however, the reaction no longer follows a single course:



(2)

Since BSD is also difficult to separate from trimethylchlorosilane, the process is less suitable for the preparation of this diimine. However, it may offer advantages in the synthesis of other diimines.

	H—N=N—H [11] yellow			
>B—N=N—B< [10] yellow	≥C—N=N—C≤ [4] yellow-red	>N—N=N—N< [12] colorless	—O—N=N—O— [13] colorless	F—N=N—F [14, 17] colorless
?	≥Si—N=N—Si≤ [3] pale blue	>OP—N=N—PO< [15] violet	$—O_2S—N=N—SO_2—$ [16] deep yellow	(Cl—N=N—F [17]) yellow

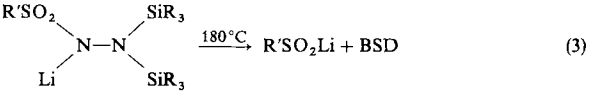
If one disregards diimine, BSD stands out from this series of azo compounds because of its unusual properties. This compound, whose preparation, structure, and reactivity will be surveyed below, reacts extremely violently with itself and with oxygen, and can ignite on contact with air. Since BSD is also readily hydrolyzed, it is not easy to handle. Most of the operations described in the next few sections must therefore be carried out at low temperatures and in the absence of oxygen and moisture.

2. Preparation

BSD can be prepared particularly easily by reaction of an arenesulfonyl azide with lithium tris(trimethylsilyl)-hydrazide in ether at −78 °C (R′ = phenyl, *p*-tolyl)[3]:

Reaction (2) is evidently initiated by attack of the silylhydrazide on the electrophilic sites of the arenesulfonyl chloride, *i.e.* the sulfur and the chlorine atom. The attack on the sulfur atom leads to elimination of lithium chloride and formation of tris(trimethylsilyl)arenesulfonohydrazide, while the attack on the chlorine atom gives lithium arenesulfinate and *N*-chlorotris(trimethylsilyl)hydrazine, which decomposes into trimethylchlorosilane and BSD.

A third method for the preparation of BSD consists in the thermolysis of *N*-lithiobis(trimethylsilyl)arylsulfonohydrazide at 180 °C:

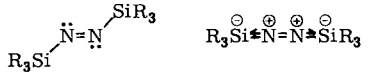


(3)

3. Structure

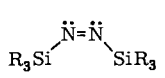
3.1. Molecular Geometry

Several structures are conceivable for BSD. The compound could contain a *trans*-angular *(5)*, *cis*-angular *(7)*, or linear *(6)* SiNNSi skeleton. In addition to 1,2-bis-(trimethylsilyl)diimine, the positional isomer 1,1-bis(trimethylsilyl)diimine *(8)* must also be considered.

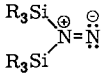


(5)

(6)



(7)



(8)

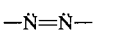
The formally charged isomeric structure *(8)* is counter-indicated by many physical properties of the compound (*e.g.* volatility, solubility) and by IR[9] and (indirectly) ESR[20] spectroscopic data (cf. Section 3.2.2). Moreover, there is no chemical evidence of the existence of *(8)* even in small equilibrium concentrations in the presence of *(5)*, *(6)*, and *(7)*[21].

A definite decision in favor of one of the three remaining isomers *(5)*, *(6)*, and *(7)* is possible only with reservations. UV spectroscopic studies[9] provide very definite evidence against the linear form (cf. Section 3.2.1), and indicate a relatively large SiNN angle (in comparison with CNN angles in organic diimines). On the basis of the geometry of trimethylsilyl isocyanate and isothiocyanate[22], this angle should be about 150° in BSD.

It is uncertain whether BSD is in the form *(5)* or *(7)*. Even at about −80 °C, the compound gives only one signal in the ^{1}H-NMR spectrum[9]. This could indicate that one isomer is thermodynamically favored or, more probably, that BSD consists of a mixture of *cis*- and *trans*-isomeric molecules undergoing fast interconversion. (Inversion on nitrogen, which generally occurs readily[23], is reported to be additionally favored in silyl-nitrogen compounds[24].)

3.2. Electronic Configuration

A typical term diagram of the inner π and n molecular orbitals of the azo group



in the ground state is shown in Fig. 1 (a)[25]. The energetically lower bonding π orbital and the two n orbitals, as can be seen from the Figure, are each occupied by two electrons, while the energetically higher antibonding π* orbital is empty. The energy difference between the two π levels is more than 6 eV in the normal case. The splitting of the two n levels, on the other hand, was a subject of uncertainty for a long time[26]. According to very recent photoelectron-spectroscopic investigations[27], the energy splitting, with a value of 3.32 eV in the case of azomethane, is surprisingly large. The lower n orbital thus lies below the bonding π orbital.

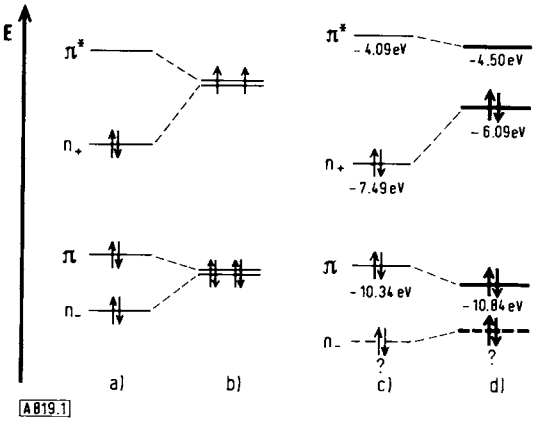


Fig. 1. Term diagram of inner molecular orbitals: a) of the angular azo group; b) of the linear azo group; c) of the azo system of bis(*tert*-butyl)diimine [29]; d) of the azo system of BSD [29].

In addition to the π and n orbitals of the azo group, it is also necessary to consider the σ and σ* molecular orbitals.

3.2.1. The Color of BSD

One of the particularly remarkable properties of BSD is its light blue color. The weak absorption that is responsible for this color, a forbidden $n_+ \rightarrow \pi^*$ transition (cf. Fig. 1 (d)), occurs at 12750 cm^{-1}, *i.e.* in the invisible infrared region of the spectrum. One "sees" only the short-wave tail of the absorption band. Thus the wavelength of the $n_+ \rightarrow \pi^*$ transition of BSD is surprisingly long in comparison with the longest-wavelength UV absorption maximum of yellow to red organic azo compounds (cf. Fig. 1 (c) and (d) and Table 1).

Table 1. UV absorptions (solvent: alkane) [9] and ionization energies (*IE*) [28] of *tert*-butyl- and trimethylsilyl-substituted diimines [29b] (R = CH_3).

	$R_3C-N=N-CR_3$	$R_3C-N=N-SiR_3$	$R_3Si-N=N-SiR_3$
color	pale yellow	red	pale blue
IE (eV)	7.49 ± 0.02	[a]	6.09 ± 0.02
$\lambda_{max}^{n_+ \rightarrow \pi^*}$ (cm^{-1}) (ε)	27200 (12)	20000 (9)	12750 (5) [b]
$\lambda_{max}^{\pi \rightarrow \pi^*}$ (cm^{-1}) (ε)	50000 (1800)	50000 (1100)	52100 (1700) [c]

[a] Accurate determination has so far been prevented by experimental difficulties. *IE* is about 7 eV.

[b] The strongly asymmetric band exhibits fine structure.

[c] Another band occurs at 40000 (260).

It can be shown experimentally that the bathochromic shift of the $n_+ \rightarrow \pi^*$ absorption of about 2×7200 wave numbers on replacement of the two "trimethylmethyl" groups in bis(*tert*-butyl)diimine by the homologous trimethylsilyl groups is due both to a pronounced increase in the n_+ energy level and to a slight decrease in the π^* energy level (cf. Fig. 1 (c) and (d)[29a]). The mechanism of this mutual approach of the levels, which has not yet been fully elucidated, could be explained, *e.g.*, by inductive and mesomeric effects[30] and by repulsion effects of bonding electrons[31] of the elements E=C and Si bonded to the azo group. It should also be observed that widening of the ENN angle must also bring the n_+ and π^* energy levels closer together.

In the extreme case of the linear skeleton $\geqq$E—N=N—E$\leqq$ (ENN angle = 180°), the n_+ and the π^* levels are in fact degenerate with each other (and the same is true of the n_- and π levels), so that the difference in the energy levels becomes vanishingly small (cf. Fig. 1 (b)). Widening of the ENN angle on replacement of *tert*-butyl groups attached to the azo group by trimethylsilyl groups is indicated by the observed decrease in the molar extinction[26] of the $n_+ \rightarrow \pi^*$ absorption (cf. Table 1).

3.2.2. The Delocalization of Electrons in BSD

Both for the occupied π orbital and for the n_+ orbital of BSD, there is a possibility of interaction with the empty d orbitals of the silicon of suitable symmetry. Nothing is known at present about the magnitude of this interaction, which can be described *e.g.* by limiting resonance structures such as

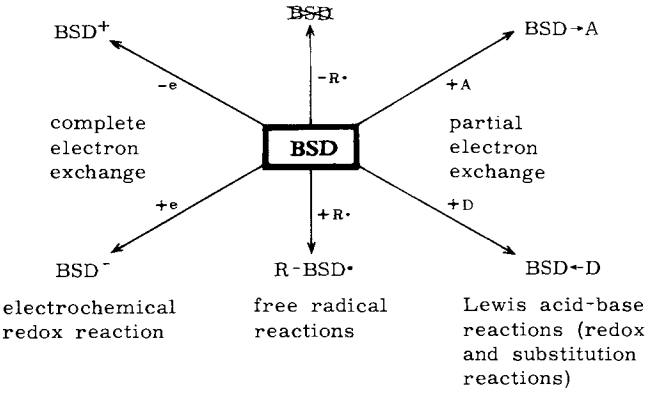
$$[\rightarrow R_3\overset{\ominus}{Si} \leq \overset{\oplus}{N}=\dot{N}-SiR_3 \leftrightarrow R_3Si-\dot{N}=\dot{N}-SiR_3 \leftrightarrow R_3Si-\dot{N}=\overset{\oplus}{N}=\overset{\ominus}{SiR_3} \leftrightarrow]$$

On the whole, a weak but definite delocalization of the π and n electrons is to be expected, since the ESR spectrum of the BSD radical-anion[20], in the case of the unpaired electron accommodated in the π^* molecular orbital, points to delocalization (though not very extensive) over the entire SiNNSi skeleton.

The ESR line-splitting diagram of the BSD radical-anion corresponds to an interaction in which the nitrogen nuclei are equivalent[20]. The anion is thus not in the unsymmetrical 1,1 form *(8)* but in the symmetrical 1,2-diimine form. This result indicates that uncharged BSD is also in the symmetrical form, and not in the equally conceivable unsymmetrical form.

4. Reactivity

BSD is extremely reactive, and reacts with practically anything available. This striking reactivity of the azosilane system can be deduced from the term diagram of the compound (Fig. 1 (d)). The inner molecular orbitals of BSD that are important to chemical reactions, *i.e.* the highest occupied n_+ molecular orbital and the lowest empty π^* molecular orbital, have very high and very low energies respectively, unlike the corresponding orbitals of the azoalkanes. This necessarily makes the compound particularly ready to give up and to receive electrons.



Scheme 1. Reactivity of bis(trimethylsilyl)diimine.

As has been confirmed experimentally, the donation or acceptance of electrons can take place completely in an electrochemical redox reaction or only partly in a Lewis acid-base reaction (a redox reaction in the broader sense). The primary reaction products obtained from BSD in this way (cf. Scheme 1) are BSD cations and anions (BSD^+, BSD^-) on the one hand and BSD-acceptor and BSD-donor complexes (BSD→A, BSD←D) respectively on the other, which can undergo further chemical reaction in most cases. For example, BSD-acceptor complexes cannot generally be isolated; one obtains only their further reaction products, which can be formally described as products of redox or substitution reactions of BSD (cf. Scheme 2, Section 4.3).

It is also to be expected that radicals R which combine the properties of an electron acceptor with those of a donor will also add to BSD to form hydrazyl radicals (R—BSD·). According to the results that we have obtained so far, this is in fact so. However, BSD is fairly stable toward free-radical cleavage of the Si—N bond resulting in destruction of the BSD molecule (~~BSD~~), which could conceivably occur from energetically excited BSD with simultaneous formation of molecular nitrogen. Thus no detectable decomposition of BSD occurs on UV irradiation for several hours, and BSD can be kept indefinitely in daylight. The compound is also very stable toward heat, provided that the molecules have no opportunity for collisions leading to rapid decomposition.

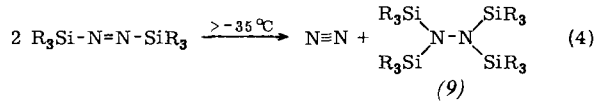
The reactions of BSD are classified according to type in Scheme 1, and numerous examples are given in the following sections.

4.1. Thermolysis Reactions

BSD decomposes below 0°C. The thermolysis products, the yields of which depend on the temperature, result from disproportionation, dimerization, and free-radical reactions of BSD.

4.1.1. Disproportionation

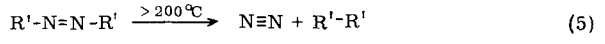
The thermolysis products formed from BSD by disproportionation between −35 and −20 °C consist almost exclusively of nitrogen and tetrakis(trimethylsilyl)hydrazine *(9)*, which was synthesized for the first time in this way[3]:



(4)

(9)

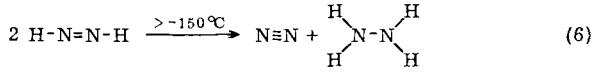
The azosilane BSD thus shows no similarity either in its thermal stability or in its decomposition mechanism to the very stable azoalkanes[32], which decomposed in a first order reaction, mainly into nitrogen and hydrocarbons:



(5)

The decomposition of BSD (4) corresponds, however, to the thermolysis of the parent diimine, which decomposes into nitrogen and hydrazine even at very low temperatures[11].

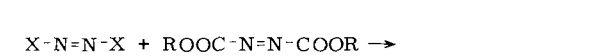
The thermolysis of BSD thus again supports the empirical observation that from the chemical point of view, silyl groups are less like organyl groups than like hydrogen. The replacement of the hydrogen atoms of diimine by silyl



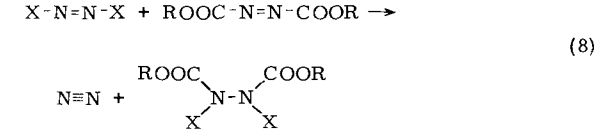
(6)

groups does not affect the stoichiometry of the decomposition of the diimine in any way, but merely leads to a considerable increase in the thermal stability of the molecule.

The similarity of the chemical properties of diimine and BSD is not confined to thermolysis. Both diimine and BSD can transfer their ligands from the azo group to a double-bond system other than their own in a reaction corresponding to the decomposition (4) or (6). For example, both compounds quantitatively reduce both oxygen[11,33] and azodicarboxylic esters[11,34] even at low temperatures, with hydrogenation and silylation respectively of the apolar double bonds (X=H, SiR_3):



(7)



(8)

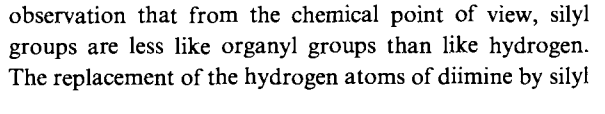
Azoalkanes, on the other hand, do not react with oxygen or azodicarboxylic esters, if one disregards the complicated reactions that take place at higher temperatures. The extremely ready oxidation (7) of BSD is the reason why bis(trimethylsilyl) peroxide can always be found among the products of reactions of BSD (*e.g.* of the thermolysis).

According to our observations so far, the transfer of ligands from the azo groups to double-bond systems, which can generally be achieved in the case of diimine as an uncatalyzed hydrogenation of apolar multiple bonds[11], is possible only with particularly reactive unsaturated systems in the case of BSD, since the thermolysis of BSD otherwise takes precedence. Thus unlike diimine[11], BSD does not react with "normal" carbon multiple bonds *e.g.* of ethylene or cyclohexene[35].

Since the disproportionation of BSD (4) has a reaction order greater than 1, the halflife of the thermolysis depends on the concentration of BSD. In very dilute solution, therefore, BSD can be kept for several days even at room temperature, and at a pressure of 0.001 torr it can be passed through pipes at 300 °C without decomposing since it is very stable toward a first order decomposition with free-radical cleavage of SiN bonds corresponding to the reaction exhibited by the azoalkanes (see above).

4.1.2. Dimerization

If the thermolysis of BSD takes place above −30 °C, tetrakis(trimethylsilyl)tetrazene *(10)* is formed as well as nitrogen and *(9)*[36] in accordance with the overall equation:



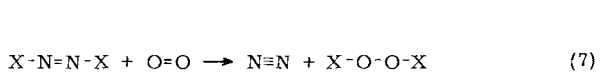
(9)

(10)

The compound *(10)*, which is the first example of a silylnitrogen compound with a four-membered nitrogen chain, is formed by a reaction path that has not hitherto been observed for azo compounds, with dimerization of BSD. The contribution of the dimerization of BSD (9) to the total reaction increases with rising temperature, partly at the expense of the disproportionation of BSD (4).

There are three conceivable routes for the formation of the tetrazene *(10)* by dimerization of BSD. These are:

1) Chain addition of two molecules of $(R_3Si)_2N{=}N$;
2) cycloaddition of two molecules of $R_3Si{-}N{=}N{-}SiR_3$ followed by rearrangement of the resulting cyclotetrazane;
3) insertion of the azo groups of two molecules of BSD into Si—N bonds in accordance with:



(10)

Since 1,1-bis(trimethylsilyl)diimine has never been detected despite attempts to intercept it[21], the first reaction path can probably be ruled out. The second reaction path is opposed *inter alia* by the Woodward-Hoffmann rules on the conservation of orbital symmetry[37], which forbid supra,supra-cycloaddition such as is to be expected here. We therefore consider the remaining reaction path (10) which may be formally regarded as a substitution reaction (cf. Section 4.4) as probable.

4.1.3. Free-Radical Reactions

With rising temperature, the thermolysis of BSD leads not only to *(9)* and *(10)* but also to increasing quantities

of tris(trimethylsilyl)hydrazine *(11)* and bis(trimethylsilyl)amine *(12)* in accordance with the overall equations[36,38]:

$$3\ R_3Si\text{-}N{=}N\text{-}SiR_3 \xrightarrow[+2\ H]{>-30\,^\circ C} N{\equiv}N + 2\ \underset{R_3Si}{\overset{R_3Si}{\diagdown}}N\text{-}N\underset{SiR_3}{\overset{H}{\diagup}} \qquad (11)$$

(11)

$$2\ R_3Si\text{-}N{=}N\text{-}SiR_3 \xrightarrow[+2\ H]{>-30\,^\circ C} N{\equiv}N + 2\ \underset{R_3Si}{\overset{R_3Si}{\diagdown}}N\text{-}H \qquad (12)$$

(12)

On the basis of equations (4), (9), (11), and (12), the silyl-nitrogen compounds are formed in yields of 21% of *(9)*, 20% of *(10)*, 28% of *(11)*, and 6% of *(12)* at 180°C with *benzene* as the thermolysis medium. The hydrogen atoms required for the formation of compounds *(11)* and *(12)* come from the methyl groups attached to the Si in BSD. The molecules that are damaged by removal of hydrogen react further to form a large number of secondary products that have not yet been investigated.

With *toluene* instead of benzene as the thermolysis medium, the hydrogen abstraction takes place exclusively from the *C*-bound methyl groups. In addition to the thermolysis products *(9)* to *(12)*, the main product found under these conditions is a hydrazone *(13)* formed in accordance with

$$4\ R_3Si\text{-}N{=}N\text{-}SiR_3 + H_3C\text{-}R' \longrightarrow N{\equiv}N + 2\ \textit{(11)} + \underset{R_3Si}{\overset{R_3Si}{\diagdown}}N\text{-}N{=}CH\text{-}R' \qquad (13)$$

(13)

(R′ = phenyl). Benzyltrimethylsilylhydrazines are also formed as by-products. From the decrease in the yield of *(9)* and the corresponding increase in the yield of *(11)* on replacement of benzene by toluene as the solvent, it can be deduced that the disproportionation of BSD (4) and the free-radical reaction of BSD (11) involve a common intermediate.

It seems possible that the reactions (4) and (11), which proceed independently of the non-radical dimerization of BSD (9), are induced by the free-radical reaction (14a).

$$BSD \xrightarrow[+BSD]{(a)} N_2 + \underset{R_3Si}{\overset{R_3Si}{\diagdown}}N\text{-}N^{\bullet}\underset{SiR_3}{\diagup} + {}^{\bullet}SiR_3 \qquad (14)$$

(b) +BSD

The tris(trimethylsilyl)hydrazyl radical formed in accordance with equation (14) could then react further with the trimethylsilyl radical, either by combining to form the hydrazine *(9)* or by hydrogen abstraction to form the hydrazine *(11)* (cf. also Section 4.3.2).

4.2. "Electrochemical" Redox Reactions

4.2.1. BSD as an Electron Acceptor and Donor

Figure 2 shows the energy levels of inner molecular orbitals of the electron acceptor tetracyanoethylene (TCNE) and of the electron donor tetrakis(dimethylamino)ethylene (TDAE), together with the corresponding orbitals of BSD. TCNE has an extremely low empty π^* orbital, and can therefore accept one or two electrons to form monoanions or dianions ($TCNE^-$, $TCNE^{2-}$)[39]. Conversely, the highest occupied π orbital of TDAE is energetically extremely high; TDAE can therefore give up one or two electrons to form monocations or dications ($TDAE^+$, $TDAE^{2+}$)[40]. Since the empty π^* orbital of TCNE and the occupied π orbital of TDAE are comparable in energy with the π^* and n_+ orbitals of BSD, BSD should possess the properties both of an electron acceptor and of an electron donor and should be capable of accepting or donating one or two electrons:

$$R_3Si\text{-}N{=}N\text{-}SiR_3 \underset{-e}{\overset{+e}{\rightleftharpoons}} R_3Si\text{-}N^{\ominus}\text{-}N\text{-}SiR_3 \underset{-e}{\overset{+e}{\rightleftharpoons}} R_3Si\text{-}N^{\ominus}\text{-}N^{\ominus}\text{-}SiR_3 \qquad (15a)$$

$$R_3Si\text{-}N{=}N\text{-}SiR_3 \underset{+e}{\overset{-e}{\rightleftharpoons}} R_3Si\text{-}N^{\oplus}\text{-}N\text{-}SiR_3 \underset{+e}{\overset{-e}{\rightleftharpoons}} R_3Si\text{-}N^{\oplus}\text{-}N^{\oplus}\text{-}SiR_3 \qquad (15b)$$

BSD does in fact readily undergo electrochemical reduction to the radical-anion BSD^-[30]. On the other hand, the expected high stability of the radical-cation BSD^+ is impressively shown by the appearance in the mass spectrum of a molecular ion signal that is unusually intense for silyl-nitrogen compounds.

The introduction of electrons into the BSD system or the withdrawal of electrons from the system should also be possible by reaction of BSD with electropositive metals or with electronegative nonmetals of the main groups. As can be seen from the following discussion, alkali and

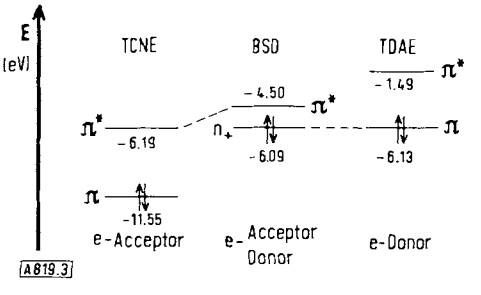


Fig. 2. Term diagram of the highest occupied and lowest unoccupied molecular orbitals of tetracyanoethylene (TCNE), bis(trimethylsilyl)-diimine (BSD), and tetrakis(dimethylamino)ethylene (TDAE).

alkaline earth metals on the one hand and halogens and chalcogens on the other react with BSD, whereas the elements of groups III, IV, and V, as well as hydrogen (in the absence of catalysts) show no reactivity toward BSD.

4.2.2. Reduction of BSD with Electropositive Metals[41]

When alkali metals in ethers are brought into contact with BSD, the quintet signal characteristic of a radical-anion BSD^- is immediately observed in the ESR spectrum[20]. For example, lithium reacts quantitatively with BSD in tetrahydrofuran (THF) at $-78\,^\circ C$ according to (16a) to give Li[BSD]:

$$BSD + Li \xrightarrow[THF]{-78\,^\circ C} Li[BSD] \qquad (16a)$$

$$BSD + 2\,Li \xrightarrow[(C_2H_5)_2O]{-30\,^\circ C} Li_2[BSD] \qquad (16b)$$

As expected, BSD can also be reduced to the dianion by alkali metals. Thus three days' reaction of BSD with lithium in diethyl ether at $-30\,^\circ C$ affords $Li_2[BSD]$ in accord with (16b).

Unlike the BSD dianion, the resulting BSD radical-anions are stable only at low temperatures, and decompose at higher temperatures, depending on the metal M and the solvent, with loss of nitrogen and formation of products that include $(R_3Si)_2NM$, $(R_3Si)_2N_2M_2$, MN_3, and $(R_3Si)_4N_2$. The course of the reaction is very complex, as can be shown for the reaction of BSD with lithium in THF, which proceeds quantitatively in accordance with

$$2\,BSD + 2\,Li \xrightarrow{THF} 2\,(R_3Si)_2NLi + N_2 \qquad (17)$$

This reaction is induced at $-60\,^\circ C$ by the formation of the compound Li[BSD] as in eq. (16a). The latter compound then decomposes in a first order reaction (with a half life of ≈ 1 hour at $-45\,^\circ C$) into nitrogen and lithium bis(trimethylsilyl)amide *(14)*.

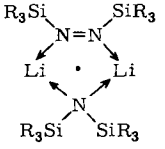
$$2\,Li[BSD] \rightarrow N{\equiv}N + 2\,\underset{(14)}{LiN(SiR_3)_2} \qquad (18)$$

However, one finds a total of only 50% conversion in accordance with equation (18), from which it follows that a reaction product (which must be *(14)*) stabilizes unreacted Li[BSD] by "complex formation".

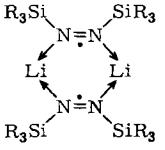
$$Li[BSD] + (14) \rightarrow \underset{(15)}{\text{"Li[BSD]·LiN(SiR}_3)_2\text{"}} \qquad (19)$$

Freshly prepared Li[BSD] accordingly does not decompose at $-45\,^\circ C$ if an equimolar quantity of *(14)* is added to the reaction solution.

Since the ESR spectrum of a solution of the complex *(15)* points to three nitrogen atoms in the molecular complex, two of which must be similarly bound, we consider the following structural formula *(15)* to be possible:



(15)



(16)

Li[BSD] evidently also forms a complex with itself (suggested formula *(16)*), since only in this way can the reaction order of 1 found for the decomposition of Li[BSD] be simply explained on the basis of an intramolecular rearrangement[42]. Complex formation of this type is also indicated by the observation that Li[BSD] is also formed from $Li_2[BSD]$ and BSD in THF.

$$Li_2[BSD] + BSD \underset{pentane}{\overset{THF}{\rightleftharpoons}} \underset{(16)}{\{LiBSD\}_2} \rightleftharpoons 2\,Li[BSD] \qquad (20)$$

Conversely, by replacement of the solvent THF by pentane, the compound *(16)* can be converted quantitatively into $Li_2[BSD]$ and BSD; the indicated equilibrium (20) is displaced completely to the left because of the insolubility of $Li_2[BSD]$ in pentane.

The concentration of free Li[BSD] in equilibrium with the complex *(15)* is evidently so small that the decomposition of the complex into nitrogen and *(14)* *via* Li[BSD]

$$2\,(15) \rightarrow N_2 + 4\,(14) \qquad (21)$$

proceeds only very slowly; the first halflife of the decomposition (21) is about 1 week at $-45\,^\circ C$. However, all the initially formed Li[BSD] ultimately decomposes in accordance with equation (18), with quantitative formation of nitrogen and lithium bis(trimethylsilyl)amide *(14)*.

It should be mentioned in passing that Li[BSD] can also be stabilized by complex formation with BSD in diethyl ether.

$$Li + 3\,BSD \xrightarrow{ether} \{Li[BSD] + 2\,BSD \longrightarrow Li(BSD)_2]^+\,BSD^- \qquad (22)$$

4.2.3. Oxidation of BSD with Electronegative Nonmetals[43]

The oxidizing power of nonmetals increases from left to right and from bottom to top of the periodic table. In agreement with this, BSD reacts with the halogens and the more strongly oxidizing chalcogens oxygen, sulfur, and selenium, but not with tellurium or the elements of group V. However, the reactions with electronegative nonmetals never led to BSD cations. This is understandable if one considers the positive charge produced on the BSD system on cation formation (cf. equation (15b)), which greatly facilitates nucleophilic substitution of the anion belonging to the BSD cation.

For example, tetrakis(dimethylamino)ethylene (TDAE) reacts quantitatively with halogen to form TDAE dihalide[40]. The reaction of BSD with halogen, on the other hand, leads not to BSD dihalide but only to its formal further reaction products, nitrogen and trimethylhalosilane.

$$TDAE + Hal_2 \rightarrow TDAE^{2+}\,2\,Hal^- \rightarrow \text{no further reaction} \qquad (23)$$

$$BSD + Hal_2 \rightarrow (BSD^{2+}\,2\,Hal^-) \rightarrow N{\equiv}N + 2\,R_3Si{-}Hal \qquad (24)$$

Corresponding to reaction (24), oxygen (cf. reaction (7)), S_8, and red selenium oxidize BSD to nitrogen.

$$BSD + 1/8\ E_8 \rightarrow N{\equiv}N + R_3Si{-}E{-}SiR_3 \quad (25)$$
E = S, Se

The rate of the oxidation reaction decreases with increasing atomic weight of the chalcogen (the same is true of the halogens), and the oxidation is increasingly suppressed by the thermolysis of BSD in the order O, S, Se, Te:

	O_2	S_8	Se_8	Te_n
% oxidation	100	47	2	0
% thermolysis	0	53	98	100

The halogenation and chalcogenation of BSD naturally need not follow the reaction (24). The reactions (24) and (25) can probably be assigned to the redox reactions, which will be discussed below.

4.3. Redox Reactions in the Broader Sense

4.3.1. BSD as a Lewis Acid and Lewis Base

The ability of BSD to act as an electron acceptor and as an electron donor, which is clear from the term diagram (Fig. 2), should also be reflected in Lewis acid and Lewis base properties. Whereas only the complete electron acceptance can be achieved preparatively in the case of electrochemical redox reactions (formation of BSD^-, BSD^{2-}), the opposite is true of the acid-base reactions, which proceed with partial electron transfer; in other words, only reactions of BSD with Lewis acids involving partial electron donation (formation of BSD→A) have so far been observed, *e.g.* the reactions of BSD with lithium ions (cf. reaction (22)) and with trinitrobenzene (λ_{max} of the CT absorption of BSD·*n*TNB : 21100 cm^{-1}), which proceed with acid-base complex formation and with EDA complex formation respectively[44,44a].

Such adducts of BSD with Lewis acids frequently cannot be isolated since they are unstable and evidently decompose for the following reasons. Lewis acids S—B generally contain basic centers B as well as acidic centers S. As a result of adduct formation between BSD and the acid S—B (=A in Scheme 1) the acidic centers nitrogen and silicon of the BSD, which initially acts as a base, are activated to such a degree that they react with the (also activated) basic centers of the reactant S—B that initially acted as the acid.

As a whole, therefore, the reaction corresponds to the addition of S—B to the azo double bond or substitution of a silyl group attached to the azo group by S. The substitution product is very often unstable, and decomposes with elimination of $R_3Si{-}S$ (cf. Scheme 2).

Typical examples are provided by the reactions of BSD with *sulfur dichloride* and *sulfur dioxide* EX_2 (X = Cl, O) to form nitrogen, sulfur, and trimethylchlorosilane or nitrogen and bis(trimethylsilyl) sulfoxylate at −78 °C. The formation of these products can be readily explained on the basis of Scheme 2:

$$R_3Si{-}N{=}N{-}SiR_3 \xrightarrow[-N{\equiv}N]{EX_2} \begin{cases} X{=}Cl: & R_3Si{-}X{+}E{+}X{-}SiR_3 \\ X{=}O: & R_3Si{-}X{-}E{-}X{-}SiR_3 \end{cases} \quad (26)$$

The reaction sequence adduct formation, addition (adduct formation, substitution, elimination) corresponds overall to reduction (oxidation) of BSD through two oxidation stages to give a hydrazine derivative (to give nitrogen):

$$\text{>N-N<} \xleftarrow{\text{reduction}} \underset{\text{BSD}}{\text{-N=N-}} \xrightarrow{\text{oxidation}} N{\equiv}N \quad (27)$$

Redox reactions of the type (27) (and also substitution reactions) are of preparative interest, since they often proceed quantitatively. Reduction and oxidation reactions will therefore now be discussed in more detail (substitution reactions in Section 4.4).

4.3.2. Reduction of BSD (BSD as Oxidizing Agent)

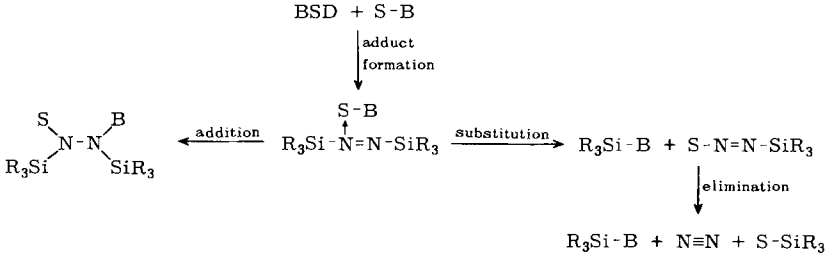
A typical addition reaction with reduction of BSD is the reaction of BSD with *organometallic compounds* (S—B = M—R′ in Scheme 2), which leads in high yields to metal bis(trimethylsilyl)organylhydrazides (M = Li, MgBr, R′ *e.g.* = methyl [cf. also reaction (52)], *n*-butyl, phenyl)[19].

$$BSD + M{-}R' \longrightarrow \begin{matrix} M & & R' \\ & N{-}N & \\ R_3Si & & SiR_3 \end{matrix} \quad (28)$$

Metal hydrides (S—B = R'_nM—H) can evidently also add to BSD, as was shown by the reaction of BSD with trimethylsilane to form tris(trimethylsilyl)hydrazine *(11)*[35].

$$BSD + R_3Si{-}H \longrightarrow \begin{matrix} R_3Si & & H \\ & N{-}N & \\ R_3Si & & SiR_3 \end{matrix} \quad (29)$$
(11)

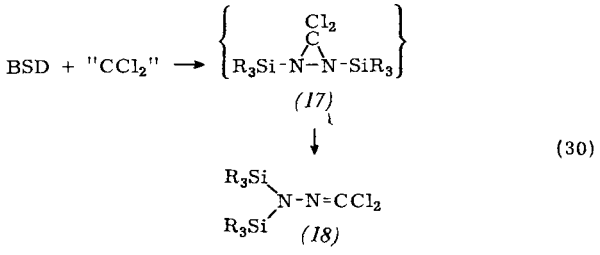
However, reaction (29) probably does not follow Scheme 2, since it proceeds in benzene only under the conditions of the thermolysis of BSD, and is completely suppressed



Scheme 2. Redox and substitution reactions of bis(trimethylsilyl)diimine.

in toluene by the free-radical thermolysis of BSD (Section 4.1.3)[45]. Trimethylsilane probably adds to BSD by a free-radical chain reaction.

Another example of the reduction of BSD is the reaction of BSD with "dichlorocarbene" formed as an intermediate from chloroform.



(30)

The product is not the expected compound *(17)*, but an open-chain isomer *(18)*. The dichlorocarbene required for reaction (30) can be formally obtained by reduction of CCl_4 with BSD (cf. Section 4.3.3); the reaction of BSD with carbon tetrachloride thus proceeds overall in accordance with equation (31)[35]:

$$2\,BSD + CCl_4 \rightarrow N_2 + 2\,R_3SiCl + \textit{(18)} \qquad (31)$$

In agreement with investigations on diimine[11], addition of a *diene* (butadiene) to BSD (Diels-Alder reaction) has not been observed.

4.3.3. Oxidation of BSD (BSD as a Reducing Agent)

We have so far found oxidations of BSD to be much more common than reductions. Many nonmetals (cf. Section 4.2.3), nonmetal halides, and nonmetal chalcogenides, as well as many other compounds, can oxidize BSD to nitrogen. This is illustrated below by some reactions of chlorides, oxides, and azides with BSD.

Reduction of Chlorides[46]

With the exception of silicon tetrachloride, all the chlorides of elements E of main groups IV–VII react with BSD. The nearer the elements of the chlorides ECl_n are to the right of the Periodic Table, the more extensively they are reduced at −78 °C in methylene chloride:

		(PCl_3)	SCl_2	ClCl
	$(GeCl_4)$	$AsCl_3$	"$SeCl_2$"	BrCl
	$SnCl_4$	$SbCl_3$	$TeCl_2$	ICl
Reduction to:	E^{II}	E^0	E^0	E^{-I}

It has also been found that in analogy with the reduction of $SnCl_4$, $TiCl_4$ is reduced to $TiCl_2$ by BSD, whereas the formally expected $GeCl_2$ is not obtained, since it evidently reacts further with BSD (cf. reaction (31)). PCl_3 is not reduced to elemental phosphorus by BSD. On the other hand, SCl_2 can be reduced to the oxidation state −II of sulfur at "higher" temperatures (0 °C, cf. reaction (25)). Selenium and tellurium were used in the form of the tetrachlorides, but the reduction of these compounds by BSD must proceed *via* the dichlorides.

The reaction of BSD with *disulfur dichloride* is particularly interesting. It leads quantitatively, in accordance with

$$2\,BSD + S_2Cl_2 \xrightarrow[-78\,^\circ C]{CH_2Cl_2} 2\,N_2 + 2\,R_3SiCl + \underset{\textit{(19)}}{R_3Si{-}S{-}S{-}SiR_3} \qquad (32)$$

to bis(trimethylsilyl)disulfane *(19)* if S_2Cl_2 is added dropwise to a cooled solution of BSD. (Similarly, reaction of BSD with *trisulfur dichloride* leads to bis(trimethylsilyl)trisulfane in a reaction resembling (32).) One possible explanation of reaction (32) could be that, corresponding to the expected reaction (26), S_2Cl_2 is first reduced by BSD to disulfur, which could then react further with BSD, in analogy with reaction (7) with oxygen, to form the disulfane *(19)*, which decomposes readily in accordance with

$$\textit{(19)} \rightarrow R_3Si{-}S{-}SiR_3 + 1/8\,S_8 \qquad (33)$$

Diselenium dichloride probably also reacts in accordance with equation (32), but instead of the expected bis(trimethylsilyl)diselane, one obtains bis(trimethylsilyl)selane and selenium (cf. reaction (33)).

The reductions of some chlorine compounds ECl_n of the nonmetals of the first short period (E = N, O, F) with BSD, which have not yet been mentioned, differ from the reactions discussed so far, since these compounds contain positive chlorine. Instead of the central element E, therefore, only the ligand chlorine can be reduced. This is clear from a comparison of the reactions of BSD with bis(organyl)chloroamine and bis(organyl)-chlorophosphane in methylene chloride:

$$BSD + R_2N{-}Cl \rightarrow N_2 + R_3SiCl + R_2N{-}SiR_3 \qquad (34)$$

$$BSD + 2\,R_2P{-}Cl \rightarrow N_2 + 2\,R_3SiCl + R_2P{-}PR_2 \qquad (35)$$

(Concerning reaction (35), cf. Section 4.4; for the reaction of BSD with CCl_4, cf. reaction (31).)

Reduction of Oxides[46]

Whereas the σ bonds of the nonmetal chlorides readily undergo reductive cleavage by BSD, this agent preferentially attacks only π bonds in the nonmetal oxides, so that the choice of possible reaction partners for BSD is smaller in the case of the oxides than in the case of the chlorides. Reduction reactions have so far been observed only for carbon, nitrogen, "oxygen", and sulfur oxides (carbon dioxide does not react with BSD). Only the reactions of BSD with sulfur oxides will be discussed below.

Sulfur dioxide, as was mentioned earlier (cf. reaction (26)), is reduced to bis(trimethylsilyl) sulfoxylate *(20)* by BSD at −78 °C[47].

$$BSD + SO_2 \rightarrow N_2 + \underset{\textit{(20)}}{R_3SiO{-}S{-}OSiR_3} \qquad (36)$$

The very unstable sulfoxylate *(20)*, which was obtained in this way for the first time, decomposes above $-40\,^{\circ}C$ into sulfur dioxide, sulfur, and hexamethyldisiloxane. In the presence of sulfur trioxide, this decomposition takes place even at $-78\,^{\circ}C$, and in this case, as expected, hexamethyldisiloxane is obtained as the SO_3 adduct, bis(trimethylsilyl) sulfate *(21)*[48].

$$(20) \xrightarrow[-1/2\,SO_2,\,-1/2\,S]{} (R_3Si)_2O \xrightarrow{+SO_3} R_3SiO{-}\overset{\overset{O}{\|}}{S}{-}OSiR_3 \quad (37)$$
$$\underset{\overset{\|}{O}}{(21)}$$

The sulfoxylate *(20)* is also formed from BSD and sulfuryl chloride, since BSD probably first reduces the chloride SO_2Cl_2 to SO_2 (cf. above),

$$BSD + SO_2Cl_2 \rightarrow N_2 + 2\,R_3SiCl + SO_2 \quad (38)$$

which then reacts further in accordance with equation (36).

Sulfur trioxide is also reduced by BSD. The reaction product to be expected here in accordance with reaction (36), *i.e.* bis(trimethylsilyl) sulfite

$$BSD + SO_3 \rightarrow N_2 + R_3SiO{-}\overset{\overset{O}{\|}}{S}{-}OSiR_3 \quad (39)$$
$$\underset{(22)}{}$$

cannot be isolated, since it appears to be thermally unstable and reacts rapidly with further sulfur trioxide in a reaction similar to (37) to form sulfur dioxide and silyl sulfate *(21)*.

$$(22) \xrightarrow[-SO_2]{} (R_3Si)_2O \xrightarrow{+SO_3} (21) \quad (40)$$

Since SO_2 can react first with BSD and then with SO_3 in accordance with equations (36) and (37), the overall reaction of BSD with sulfur trioxide ultimately corresponds to the formation of nitrogen, sulfur, and bis(trimethylsilyl) sulfate *(21)*.

$$3\,BSD + 4\,SO_3 \rightarrow 3\,N_2 + S + 3\,(21) \quad (41)$$

Sulfur monoxide, which should occur as an intermediate in the reaction of BSD with thionyl chloride (cf. reaction (38)), should also react with BSD in the same way as oxygen (reaction (7)):

$$BSD + \text{"SO"} \xrightarrow{?} N_2 + R_3Si{-}S{-}O{-}SiR_3 \quad (42)$$
$$\underset{(23)}{}$$

However, the reaction of thionyl chloride with BSD leads not to the compound *(23)*, but to products that include sulfur and hexamethyldisiloxane (formally the decomposition products of the compound *(23)*) in accordance with

$$2\,BSD + SOCl_2 \rightarrow 2\,N_2 + 2\,R_3SiCl + 1/8\,S_8 + (R_3Si)_2O \quad (43)$$

Like SCl_2, therefore, SO is reduced to sulfur. The fundamental possibility of reaction of element-oxygen groups with BSD in the sense of reaction (42) is strongly indicated by the reaction of BSD with *nitrosobenzene*:

$$BSD + Ph{-}N{=}O \rightarrow N_2 + R_3Si{-}\overset{\overset{Ph}{|}}{N}{-}O{-}SiR_3 \quad (44a)$$

or with *benzophenone*:

$$BSD + 2\,Ph_2C{=}O \rightarrow N_2 + Ph_2\overset{\overset{R_3SiO}{|}}{C}{-}\overset{\overset{OSiR_3}{|}}{C}Ph_2 \quad (44b)$$

Reduction of Azides[49]

Finally, the reactions with azides to form amines also merit attention among the oxidations of BSD:

$$BSD + X{-}N_3 \rightarrow 2\,N_2 + X{-}N(SiR_3)_2 \quad (45)$$

Since BSD reacts only with electrophilic azides XN_3 below $0\,^{\circ}C$ (X = *e.g.* acyl, *p*-toluenesulfonyl[50], $(RO)_3Si$[51], but not phenyl, R_3Si) and the rate of the reaction (45) is increased by polar reaction media, (45) is probably induced by electrophilic attack of the azide on the azo system (formation of the adduct *(24)*) in accordance with the general reaction Scheme 2. *(24)* could then readily change into the observed products by migration of silyl groups.

$$X{-}N{=}N{-}\overset{\uparrow}{N}{=}N{-}SiR_3 \rightarrow X{-}N\begin{matrix}SiR_3\\SiR_3\end{matrix} + 2\,N{\equiv}N \quad (46)$$
$$\underset{(24)}{R_3Si}$$

Hydrazoic acid also reacts with BSD in accordance with equation (45) (X = H); in this special case, however, the reaction could also be initiated by attack on BSD by a proton (cf. Section 4.4).

4.4. Substitution Reactions

4.4.1. BSD as "Azo-ation" Agent

Corresponding to the general Scheme 2 of the reaction of BSD with Lewis acids S—B, BSD substitution reactions proceed in accordance with equations (47) and (48).

$$R_3Si{-}N{=}N{-}SiR_3 + S{-}B \rightarrow R_3Si{-}B + S{-}N{=}N{-}SiR_3 \quad (47)$$
$$\underset{(25)}{}$$
$$S{-}N{=}N{-}SiR_3 + S{-}B \rightarrow R_3Si{-}B + S{-}N{=}N{-}S \quad (48)$$
$$\underset{(26)}{}$$

Such reactions thus correspond to transfer of the azo group to S; BSD thus acts as an "azo-ation agent" for S, and could therefore be used for the preparation of inorganic azo compounds *(25)* and *(26)*. However, the substituted diimines expected according to equations (47) and (48) are frequently not obtained, since they are often unstable and *e.g.* lose nitrogen (cf. Section 4.3) or react further with BSD (cf. Sections 4.4.2 and 4.4.3).

Thus the *protolysis* of BSD (S—B in Scheme 2 = H—X; X = *e.g.* OH, OR, $OSiR_3$, NH_2, NHR, N_3, Cl, SO_4H) leads not to diimine, which is probably formed as an intermediate in accordance with

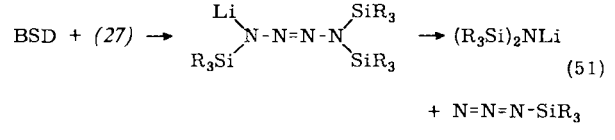
$$BSD + 2\,H{-}X \rightarrow 2\,R_3Si{-}X + H{-}N{=}N{-}H \qquad (49)$$

but to nitrogen and hydrazine (in the form of its HX adduct) together with other products (cf. Section 4.4.3). The reaction of BSD with *methyllithium* (S—B = Li—R), which proceeds with simultaneous addition (Section 4.3.2) and substitution, leads not to the expected substitution product lithium trimethylsilyldiimide, which is undoubtedly formed as an intermediate

$$BSD + Li{-}R \rightarrow R_3Si{-}R + \underset{(27)}{Li{-}N{=}N{-}SiR_3} \qquad (50)$$

but to lithium azide and lithium bis(trimethylsilyl)amide. Both compounds may be formally regarded as products formed by further reaction of the azo compound *(27)*[19].

On consideration of reaction (28) and the thermolysis and hydrolysis reactions of silylated diimines summarized in Scheme 3 (cf. Section 4.4.3), it seems particularly probable to us that the diimide *(27)* adds to BSD to form a tetrazene compound, which then decomposes:



$$BSD + (27) \rightarrow \quad \rightarrow (R_3Si)_2NLi + N{=}N{=}N{-}SiR_3 \qquad (51)$$

According to our results[52], the trimethylsilyl azide formed would react rapidly with methyllithium to give tetramethylsilane and lithium azide, so that including equations (50) and (51), the reaction course found experimentally can be represented by:

$$2\,BSD + 2\,LiR \rightarrow 2\,R_4Si + LiN_3 + (R_3Si)_2NLi \qquad (52)$$

In the reaction of BSD with *bis(organyl)chlorophosphanes* (S—B = R'_2P—Cl), instead of the azo compound *(28)* that is expected according to equation (47), and which, according to experimental results, is probably formed as a reaction intermediate:

$$BSD + R'_2P{-}Cl \rightarrow R_3Si{-}Cl + \underset{(28)}{R'_2P{-}N{=}N{-}SiR_3} \qquad (53)$$

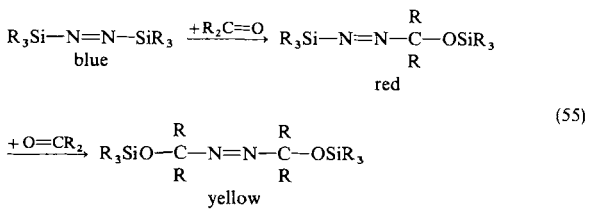
one again finds only its further reaction products (cf. Section 4.4.2).

On the other hand, the reaction of BSD with *diphenylboron chloride* (S—B = Ph_2B—Cl) proceeds as expected in accordance with equations (47) and (48).

$$BSD + 2\,Ph_2B{-}Cl \rightarrow 2\,R_3Si{-}Cl + \underset{(29)}{Ph_2B{-}N{=}N{-}BPh_2} \qquad (54)$$

This reaction allowed the preparation of the first pure azoborane *(29)*[10].

Insertion of the carbonyl group of *acetone* (S—B = $R_2C{=}O$) into the Si—N bond of BSD also occurs in the sense of reactions (47) and (48):



(55)

The reactions of BSD with organylchlorophosphanes and with water will now be discussed as examples of BSD substitution reactions in more detail.

4.4.2. Reaction of BSD with Organylchlorophosphanes[46]

The reactions of BSD with organylchlorophosphanes are sometimes rather complicated. The ease with which they proceed increases with the degree of chlorination of the phosphorus, *i.e.* with increasing acidity of the reactant. Thus triphenylphosphane does not react with BSD; diphenylchlorophosphane reacts at −30 °C, phenyldichlorophosphane reacts slowly at −78 °C, and phosphorus trichloride is violently attacked by BSD at −78 °C. The nature of the reaction products is strongly dependent on the reaction medium as can be illustrated for the reaction of *bis(organyl)chlorophosphanes* with BSD.

With *methylene chloride* as the solvent, bis(organyl)chlorophosphanes react to form tetrakis(organyl)diphosphanes

$$BSD + 2\,R'_2P{-}Cl \xrightarrow{CH_2Cl_2} N_2 + 2\,R_3Si{-}Cl + R'_2P{-}PR'_2 \qquad (56)$$

The reaction proceeds in accordance with equation (53) *via* a phosphanoazo compound *(28)*, the formation of which can be correlated with a deep green-blue color that appears during the reaction. According to our investigations so far, *(28)* decomposes with liberation of nitrogen.

$$\underset{(28)}{R'_2P{-}N{=}N{-}SiR_3} \rightarrow N{\equiv}N + R'_2P{-}SiR_3 \qquad (57a)$$

The bis(organyl)trimethylsilylphosphane (which can be isolated in the case of R′ = mesityl) finally reacts with bis(organyl)chlorophosphane as follows[52].

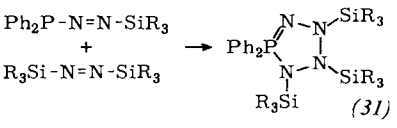
$$R'_2P{-}SiR_3 + Cl{-}PR'_2 \rightarrow R_3Si{-}Cl + R'_2P{-}PR'_2 \qquad (57b)$$

With *diethyl ether* as the solvent, bis(organyl)chlorophosphanes react much more slowly than in methylene chloride. The product obtained on reaction of BSD with diphenylchlorophosphane is tris(trimethylsilyl)diphenylphosphamidine *(30)* which can then react further with an excess of

$$2\,BSD + Ph_2P{-}Cl \xrightarrow{ether} N_2 + R_3Si{-}Cl + \underset{(30)}{Ph_2P(=N(SiR_3))(N(SiR_3)_2)} \qquad (58)$$

diphenylchlorophosphane (*e.g.* to form $[Ph_2P{-}Ph_2P{=}N{-}PPh_2{=}N{-}\overset{\oplus}{P}Ph_2{-}PPh_2]Cl^{\ominus}$). This reaction leads surprisingly to a compound with isolated nitrogen atoms. The diimine group must therefore have been split during the formation of *(30)*.

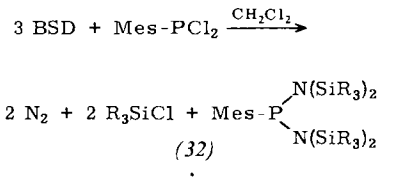
We assume that the reaction (58) again proceeds first *via* the phosphanoazo compound *(28)* in accordance with equation (53) (R′ = phenyl), and that *(28)* then undergoes "1,3-dipolar" addition with BSD, as in related cases[53,54], with formation of the adduct *(31)*:



(59)

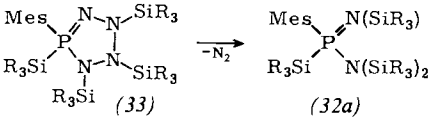
The compound *(31)* could decompose, after migration of two silyl groups to phosphorus-bound nitrogen atoms, into the final products, *i.e.* nitrogen and *(30)*.

Reactions of BSD with organyldichlorophosphanes or even with phosphorus trichloride are even more complicated than those with bis(organyl)chlorophosphanes. This is connected with the greater number of reactive chlorine atoms. For example, the reaction of BSD with *mesityldichlorophosphane* leads *inter alia* to the phosphane *(32)*:



(60)

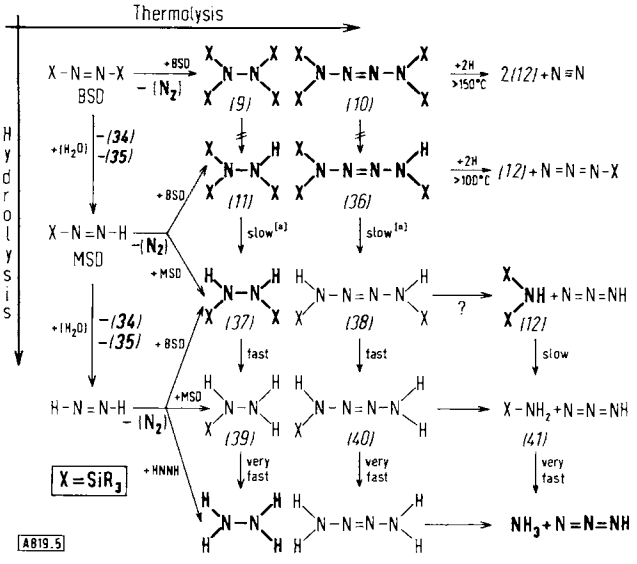
The formation of *(32)* can be readily explained on the basis of the earlier discussions. Mesityldichlorophosphane first undergoes a reaction corresponding to the sequence of equations (53), (56) to give $Mes(R_3Si)PCl$, which reacts further with BSD in accordance with the sequence (53), (59) to give compound *(33)*. Like *(31)*, compound *(33)* can then decompose to form a phosphamidine *(32a)*, which would rearrange into the final product *(32)*.



(61)

4.4.3. Reaction of BSD with Water[35]

When BSD is brought into contact with water at 20–40 °C, the reaction products include tetrakis(trimethylsilyl)hydrazine *(9)*, tetrakis(trimethylsilyl)tetrazene *(10)*, hydrazine, ammonia, and ammonium azide, as well as nitrogen, trimethylsilanol R_3SiOH *(34)*, and the condensation product of the latter $(R_3Si)_2O$ *(35)*. A detailed investigation of the hydrolysis of BSD showed that the reaction of BSD with water takes place in two main reaction steps, which differ greatly in their rates. Several fast reactions first lead to the products shown in bold type in Scheme 3, which can be detected as such (reaction time for the *primary hydrolysis*: a few hours). Apart from bis(trimethylsilyl)hydrazine *(37)*, which reacts further with water even during the primary hydrolysis, some of these compounds, *i.e.* *(11)*, *(36)*, and *(12)*, are slowly hydrolyzed to hydrazine, ammonia, and ammonium azide with formation of *(34)* and *(35)* (reaction time for the *secondary hydrolysis*: a few weeks).



Scheme 3. Hydrolysis of bis(trimethylsilyl)diimine.
[a] Hydrolysis leads to 1,1-bis(trimethylsilyl)hydrazine and tetrazene.

The following observations should be added in connection with Scheme 3. *(9)* and *(10)* are formed by thermal disproportionation and dimerization of BSD with itself (Section 4.1). The formation of *(11)* and *(36)* can also be explained by corresponding reactions of BSD with mono(trimethylsilyl)diimine (MSD)[55]. It may therefore be assumed that the hydrolysis of BSD (as expected) proceeds *via* MSD as an intermediate. MSD then reacts on the one hand with BSD by disproportionation and dimerization to give nitrogen, *(11)*, and *(36)* (predominating principal reaction), and on the other with water to give diimine. The relationship of the reactions of BSD with BSD and of BSD with MSD is particularly clearly shown by a feature of the reaction (cf. Section 4.1.2), *i.e.* the increase in yield both of tetrazene *(10)* and of *(36)* with rising reaction temperature. The decomposition of diimines by two pathways (disproportionation, dimerization), which was first observed in the thermolysis of BSD, is thus evidently of more general importance.

Whereas *(9)* and *(10)* react only unmeasurably slowly with water[56], *(11)* and *(36)* are hydrolyzed slowly but measurably to hydrazine and ammonium azide respectively (secondary hydrolysis). The unexpected formation of ammonium azide can be explained as follows: The silyltetrazene *(36)* is hydrolyzed to tetrazene, which decomposes in turn, with migration of hydrogen, into ammonia and hydrazoic acid (= ammonium azide)[36,57]. The fundamental possibility of such a decomposition is shown *e.g.* by the thermolysis of *(36)*, which leads quantitatively to *(12)* and trimethylsilyl azide above 100 °C[35].

Contrary to expectation, *(10)* does not decompose in a similar manner into tris(trimethylsilyl)amine and trimethylsilyl azide, but gives *(12)* and nitrogen above 150 °C. This free-radical decomposition, which corresponds to the

thermolysis of organic tetrazenes[12], is probably due to the fact that decomposition with migration of silyl groups is impossible on steric grounds, as was shown by examination of the Stuart model of *(10)*. The tetrazene *(38)*, which has not yet been isolated as such, should decompose in the same way as the tetrazene *(36)*, though more rapidly because of the comparatively lower steric hindrance.

Since the compounds *(11)* and *(36)* undergo only very slow hydrolytic decomposition and no thermolysis under the reaction conditions, neither of these compounds can be the source of the small quantities of hydrazine and of ammonium azide formed in the primary hydrolysis. However, initially formed hydrazine and ammonium azide could be further reaction products of the doubly silylated hydrazine *(37)* and tetrazene *(38)*. According to the above arguments, both compounds should be formed from diimine (the final product of the hydrolysis of BSD by the "direct" route) and BSD with disproportionation and dimerization. It has in fact been possible to show the probable presence, as a reaction intermediate at the beginning of the hydrolysis of BSD, of the 1,2-isomer *(37)* of bis(trimethylsilyl)hydrazine, which is itself sensitive to water[58]. On the other hand, attempts to find bis(trimethylsilyl)tetrazene *(38)* have so far been unsuccessful. The hydrolysis (and possibly also the thermolysis or a reaction with BSD) of this tetrazene is evidently so fast that only its decomposition products are found.

The compounds *(37)* and *(38)* could be formed from two molecules of MSD. However, since the concentration of the very reactive MSD probably remains small during the hydrolysis, this reaction probably makes only an insignificant contribution to the process as a whole. For the same reasons, reaction of diimine with MSD or diimine is also less likely[59].

On the whole, therefore, the reaction of BSD with water is a complicated system of successive and simultaneous hydrolysis, disproportionation, nitrogen chain degradation, and nitrogen chain formation reactions. The situation is further complicated by the fact that ammonium azide and hydrazoic acid can also react with BSD in protolysis (Section 4.4.1) or redox reactions (Section 4.3.3). The latter reaction is probably responsible in particular for the formation of ammonia (*via (12)* and its hydrolysis).

5. Outlook

It can be seen from this report that the reactive azosilane BSD has diverse and unusual chemical capabilities as a redox system and as an acid-base system, which have presented us, and will probably continue to present us, with many unexpected reactions (consider, *e.g.*, BSD as a complex ligand). The observation that the chemical behavior of BSD is similar to that of diimine also deserves special interest in this connection. It appears that the change in properties on transition from nitrogen-hydrogen compounds to their silyl derivatives is only slight, so that the latter offer "thermally stable" model compounds for the investigation of the reactions of "thermally labile" nitrogen-hydrogen compounds.

Thus, to give another example, tetrazene (N_4H_4) could conceivably decompose into:

1) Hydrazine and nitrogen ($\rightarrow N_2H_4+N_2$);
2) Diimine ($\rightarrow 2\ N_2H_2$);
3) Ammonia and hydrazoic acid ($\rightarrow NH_3+HN_3$).

The thermolysis and hydrolysis of silyltetrazenes (Section 4.4) now point to the third possibility, and oppose the thermodynamically favored first possibility, whereas the second reaction, according to results obtained so far (Sections 4.1 and 4.4) can probably proceed only in the reverse direction.

Our assumption of a close chemical relationship between silyl-substituted and unsubstituted nitrogen-hydrogen compounds offers encouragement to prepare and investigate other silylnitrogen-hydrogen compounds, which should also be ideal starting materials for the synthesis of "naked" nitrogen-hydrogen compounds. Since feasible methods for the preparation of such silyl derivatives, according to preliminary results, again lead *via* BSD, our fascinating "BSD adventure" has certainly not yet reached the limit of its possibilities.

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[2] Abbreviated hereafter to BSD; R in all formulas is CH_3.

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[46] *N. Wiberg* and *G. Schwenk*, to be published.

[47] Ozone, which is homologous with SO_2, reacts with BSD at –78 °C to form nitrogen, R_3SiOH, and $(R_3Si)_2O$. It is possible that, in analogy with reaction (36), the compound $R_3Si—O—O—O—SiR_3$ is formed first, and this would then decompose into $(R_3Si)_2O$ and singlet oxygen, which itself reacts with BSD.

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[55] Under the hydrolysis conditions (20–40 °C), only small quantities of *(11)* and vanishingly small quantities of *(12)* are formed by thermolysis of BSD. Most of the *(11)* and *(12)* that are produced in large quantities during the hydrolysis must therefore be formed in some other way.

[56] *(9)* and *(10)* are also hydrolyzed to hydrazine and ammonium azide by aqueous acids [36].

[57] Accordingly, hydrolysis intermediates such as *(38)* or *(40)* could decompose into hydrazoic acid and silylamines *(12)* and *(41)*, which hydrolyze further to form ammonium azide.

[58] The hydrazine *(37)* is formed in large quantities in the protolysis of BSD with a little ammonia.

[59] According to literature data [11], the thermolysis of diimine should lead only to nitrogen and hydrazine, so that the formation of ammonium azide is apparently due not to the decomposition of diimine, but necessarily to the hydrolysis of the silyltetrazenes *(38)* and *(40)*.

Biological Membranes

By Werner Gross[*]

Membranes are essential components of living cells. They act as barriers and pumps, as enzyme supports, and also as a means of protection. Their chemical makeup from proteins, lipids, carbohydrates, ribonucleic acids, and water is well known, but there is as yet no generally accepted model for their structure. It is also by no means certain that all membranes have the same structural plan.

1. Introduction

Membranes are structures of universal occurrence in living nature. All cells, even those of the most primitive microorganisms, are enclosed by a plasma membrane. Since the biochemical reactions taking place in the cytoplasm require a constant environment, the intracellular space must be separated from the extracellular space. The cell organelles, such as nuclei, mitochondria, and vacuoles, are also enclosed by membranes. The reaction spaces (compartments) separated in this way by membranes differ qualitatively and quantitatively in the substances that they contain; it must therefore be concluded that all membranes possess selective permeability. However, further generalizations appear to be possible only within limits, in view of the morphological and chemical differences between the membranes.

The plasma membranes of liver cells and of erythrocytes have been investigated in some depth, whereas less is known at present about the membranes of the microorganisms. The investigations on function and on structure are closely linked. Results of functional studies led to certain requirements regarding the membrane architecture, and morphological results contributed to an understanding of functional processes. Morphological views and biochemical and physiological studies have contributed in a similar manner to the current picture of biological membranes. A number of monographs and reviews on this rapidly growing field of research have been published[1-13].

Physical methods of investigation (IR, NMR, and ESR spectroscopic and X-ray analysis) have been used to a particularly large extent in the study of the components of membranes and their interactions. Since lipids and proteins do not usually give ESR signals, these membrane components must be labeled with synthetic organic radicals such as 3-maleimido-2,2,5,5-tetramethylpyrrolidin-1-oxyl[14] or nitroxide[15]. Spin labeling can be introduced into thiol and amino groups of the proteins by means of the first of these radicals, and into fatty acids and cholesterol by the second.

Increasing use is also being made of optical rotatory dispersion and circular dichroism measurements[16], and investigations based on differential thermal analysis[17] have shown that phase transformations occur in phospholipids even in physiological temperature ranges[18,19]. As a result of these methods, important conclusions have recently been drawn concerning the behavior of individual membrane components, interactions between similar and different molecules, and their phase. By refined preparation methods and the use of new detergents for solubilization, it has been possible to isolate membranes and membrane fragments that yielded more reliable analytical results. This has led to a considerable increase in knowledge of the pattern of structural components in biological membranes.

Growing numbers of investigations are being carried out on microorganisms, which offer the following advantages over animal cells. (a) Some microorganisms have no intracellular structures that could lead to serious contamination during the isolation of their plasma membrane, apart from mesosomes. (b) The concentration of certain membrane proteins can be varied by induction and repression of the protein synthesis. This offers the possibility of labeling these proteins by incorporation of radioactive amino acids and isolating them[20]. (c) The composition of certain membranes can be modified experimentally. Thus a mutant of *E. coli* that requires fatty acids for growth and that incorporates them into its membrane has been isolated[21]. In yeast, the pattern of the mitochondrial lipids depends on the partial pressure of oxygen during growth[22]. The plasma membrane of *Mycoplasma laidlawii* is rich in lipids[23]; its composition is determined by the nature of the culture medium. Extreme membrane compositions have been found for halophilic bacteria[24].

2. Properties of Biological Membranes

It has been assumed since the turn of the century that a submicroscopic lipid layer surrounds the cell and separates the cytoplasm from the extracellular space. This assumption is based in part on the work of *Overton*[25] on the ability of lipophilic and hydrophilic substances to penetrate into the cell. The dependence of the rate of penetration of a substance on its lipid solubility was later confirmed by the classic experiments carried out by *Collander*[26] on the cells of *Chara* plants. Determinations of the erythrocyte surface area and the area that was required by the lipids extracted from the membrane showed that the area occupied by the lipids was twice as large as the erythrocyte surface area. *Gorter* and *Grendel*[27] concluded from their results that the erythrocyte surface is formed by a bimolecular lipid layer.

The views on the molecular arrangement of the lipids within biological membranes were derived from what is

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known about the behavior of such substances at interfaces. During the 1930's, *Danielli* and *Davson*[28] described a membrane model in which the membrane is assumed to consist of lipids and proteins. Their model was modified more than two decades later by *Robertson*[29] on the basis of electron-microscopic observations (concept of the "unit membrane").

The surface tensions found for cells in aqueous media are small (around 1 erg/cm^2). The surface tension of a droplet of fat is 70 times as great. Absorption of proteins on such droplets of fat causes a considerable decrease in the surface tension, so that it seems reasonable to assume that proteins are present on the cell surface. Though this is correct, such a conclusion does not necessarily follow. A bimolecular lipid layer should behave differently from a droplet of fat, since compensation of the opposing tensions occurs in a bimolecular layer, and the difference may be very small[30]. Since the surface tension is not constant, but depends on the pressure, elastic properties can be ascribed to the cell surface. This elasticity points to the presence of proteins, since a pure lipid layer would not be elastic[31].

Strong arguments in favor of the existence of a substantially continuous lipid layer are provided by investigations on the electrical properties. Biological membranes have a high electrical resistance. For plasma membranes, the value varies between 10^3 and 10^5 ohm·cm^2. After damage to the membrane or during stimulation, the conductivity is increased by a few orders of magnitude[32], since the ion permeability in the affected regions of the membrane is changed. (For conflicting interpretations of the electrical phenomena, see [33].) Synthetic membranes have an even higher electrical resistance, which can be reduced by two to four orders of magnitude by substances such as the "excitability inducing material" (EIM)[*], the cyclodepsipeptides, and the polyene antibiotics. Thus EIM causes a decrease in resistance from 10^8 to 10^4 ohm·cm^2[34]. The electrical capacity of the cells is about 0.5 to 1.0 μF/cm^2.

Plant cells and microorganisms are additionally surrounded on the outside by a cell wall, whose chemical composition is different from that of the cell membrane[8]. A clear separation of the cell wall and the cell membrane is possible in gram-positive bacteria. If the cell wall of *B. megaterium* is dissolved in an isotonic sucrose solution by lysozyme, spherical protoplasts are formed[35]. When the osmolarity is reduced, the protoplasts burst, and the remaining membranes can be isolated. It has been shown conclusively by permeability investigations on such protoplasts that the membrane, and not the wall, forms the osmotic barrier between the intracellular and the extracellular spaces. It was shown in the case of isolated plasma membranes of *E. coli* that such membrane preparations are biologically intact. These membranes, which are closed to form vesicles, can accumulate certain amino acids in the interior of the vesicles[36]. After the removal of the cell contents had been achieved in a number of cases, several functions could be definitely assigned to the plasma membrane. In the case of erythrocytes, it was possible to remove the cell contents by reverted hemolysis[37]. The cell contents were squeezed out of giant nerve fibers and replaced by solutions of known composition. The action potential was recognized in this way as a membrane function[38].

[*] EIM is probably a protein.

3. The Ultrastructure of Biological Membranes

Since the 1950's, increasing use has been made of the electron microscope in the investigation of biological membranes[29, 39–45]. The plasma membrane of an erythrocyte is 80—100 Å thick. Imaging in the electron microscope after fixation with osmium tetroxide or potassium permanganate shows a trilaminar structure (Fig. 1), *i.e.* two outer dark lines, in which the fixing medium has deposited,

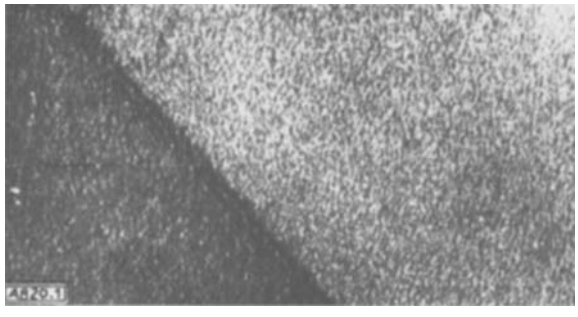


Fig. 1. Surface of a human erythrocyte. Electron micrograph after fixation with permanganate (from [29], p. 3). The trilaminar structure of the plasma membrane is clearly visible. Magnification: 280000 ×.

separated by a central light zone. This sandwich structure has been found for several membranes, and this was therefore postulated to be a general structural principle. This concept of the "unit membrane" is a further development of the Danielli-Davson model (the differences between the two models will be discussed in Section 7).

A favored object for investigation was the myelin sheath of the nerve fibers, though myelin probably occupies a special position in its chemical composition. The birefringence of the myelin sheath was discovered as early as the 1930's, and it was assumed to consist of alternating lipid and protein layers[46, 47]. It is now known that the myelin sheath develops from the plasma membrane of the Schwann cell (Fig. 2), the mesaxon being wound up in a

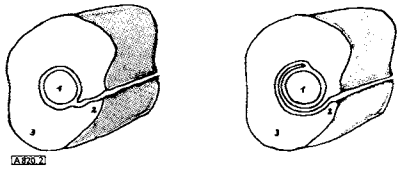


Fig. 2. Development of the myelin sheath (highly schematized). The myelin sheath develops from the plasma membrane (gray) of the Schwann cell. 1 = axon; 2 = mesaxon; 3 = Schwann cell. Left: initial stage of development; right: intermediate stage.

spiral and the individual layers then coalescing. It was found from the thickness of the repeating units that there is probably no other material enclosed between the lamellas. X-ray diffraction studies have confirmed these assumptions concerning the myelin structure.

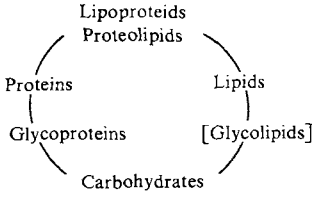
More recent findings have cast doubt on the postulate of a general structural principle of biological membranes.

Sjöstrand[48] showed with the aid of high-resolution electron micrographs that several membranes, including those of the endoplasmic reticulum, exhibit a granular ultrastructure. Further conclusions follow from the picture of the inner mitochondrial membrane[2]. Liver cell membranes exhibit a globular structure after treatment with ethylenediaminetetraacetic acid. Plan views show a characteristic hexagonal pattern, which suggests that they are built up from subunits[49].

Despite the ease with which biological membranes can be imaged, conclusions concerning the actual structure on the basis of electron micrographs are associated with some uncertainty; this situation has frequently been discussed in detail. Little is known about the reactions of the fixing medium with the membrane components. It would be premature to take it as certain that OsO_4 reacts only with proteins or that the original protein conformation could not be altered[50]. The fixation does not necessarily "freeze in" the morphological situation. Crosslinks produced by the fixing agent between proteins could change the position of the latter within the membrane. Removal of water can also lead to changes in state or influence the interactions between the membrane components. Considerable differences were discovered on measurement of the thicknesses of various membranes. However, the determinations were complicated by the fact that the membranes cannot always be clearly delimited and that the results depend on the fixing method. New paths are now being followed with the freeze-etching technique. The electron-microscopic investigations have contributed considerably to present-day views on membrane architecture. However, the question of the importance to be placed on individual items of evidence must go unanswered for the present.

4. Membrane Components

In order to determine the chemical composition, it is necessary to obtain pure membranes. Isolation is facilitated by the use of labeling enzymes (see Section 4.1.2). The components of biological membranes are proteins, lipids, water, ribonucleic acids, and covalently bound carbohydrates. Scheme 1 illustrates the relations between the combined components.



Scheme 1. Position of the combined membrane components. Lipoproteins and proteolipids differ in their solubility. The glycolipids belong to the group of lipids.

4.1. Proteins

Classification of the membrane proteins is difficult. Despite fluid transitions, three groups can be distinguished; these are transport proteins, enzymes, and structural proteins.

4.1.1. Transport Proteins

These are mostly proteins that bind substances having low molecular weights in a specific manner. In some cases they have been broken down into several binding components. If gram-negative bacteria are transferred from a sugar solution of high osmolarity into a salt solution of low osmolarity, about 5% of the membrane proteins pass into solution[51]. Some of these solubilized proteins exhibit enzymatic activity, while others have characteristic binding specificities without catalytic function *in vitro*. Some of these "dumb" proteins are probably involved in transport processes[52–54]. These proteins, which have recently been very intensively studied, are listed in Table 1. Their molecular weights are around 30000.

Table 1. Membrane proteins that are probably involved in transport processes. The proteins were isolated almost exclusively from microorganisms.

Membrane protein	Molecular weight	Ref.
Sugar transport:		
M-protein (galactosides)	31000	[20]
Heat-stable protein	9400	[55]
β-Galactoside permease	—	[56]
Galactose-binding protein	—	[57]
Galactose-binding protein	35000	[58]
Galactose carrier	—	[59]
Glucose-6-phosphate-binding protein	—	[60]
Glucose-binding protein	—	[61]
L-Arabinose-binding protein	32000	[62]
L-Arabinose-binding protein	35000	[63]
Amino acid transport:		
Leucine-binding protein	34000	[64]
Leucine-binding protein	36000	[58]
Leucine-binding protein	37000	[65]
Arginine-binding protein	—	[66]
Tryptophan-binding protein	>200000	[67]
Histidine-binding protein	—	[68]
Phenylalanine-binding protein	—	[69]
Ion transport:		
Sulfate-binding protein	32000	[70]
Calcium-binding protein	25000–28000	[71]
Phosphate-binding protein	—	[72]

4.1.2. Enzymes

Many enzymes are components of membranes or are associated with them. They are either located exclusively in the membrane (marker enzymes) or they are at least more highly concentrated in the membrane than in the adjoining parts of the cell.

Contamination of the membranes cannot be ruled out in every case. Some of the enzymes have been isolated only with difficulty. Even lipid extractions led to a loss of activity, but this could be partly reversed by addition of phospholipids. Cytochrome oxidase, succinate dehydrogenase, and β-hydroxybutyrate dehydrogenase can be reactivated in this way.

Benedetti and *Emmelot*[49] investigated liver cell membranes and found 24 enzymes, including a Na^+-K^+-stimulable adenosine triphosphatase, a *p*-nitrophenyl phosphatase, and a phosphodiesterase. Enzymes were also located histochemically in some cases[73].

4.1.3. Structural Proteins

A protein obtained from the membrane of erythrocytes has been described in detail as a structural protein[74]. This protein could be resolved into fractions by electrophoresis

at pH 9. *Criddle et al.*[75] have prepared a structural protein from bovine heart mitochondria that is insoluble in water and accounts for about 40% of the total protein. Though several arguments indicate that it is homogeneous, this has not yet been proved. This structural protein forms complexes with other mitochondrial proteins. *Woodward* and *Munkres*[76] characterized a mitochondrial structural protein from *Neurospora*. The mitochondrial structural proteins are probably essential to the full activity of the respiratory chain. Structural proteins have also been detected in other membranes, and their apparently universal occurrence suggests a general function.

4.2. Lipids

Several synopses of the lipid composition of membranes and cell organelles have been published (*e.g.*[77]). The ratio of the quantity of lipids to the quantity of proteins varies considerably from one membrane to another. Thus the lipid content of myelin[*] is about 70%, that of the mitochondria[*] is only about 30%, and that of the endoplasmic reticulum is about 50%. The lipid composition also differs[78]. In the membranes of the mitochondria and microsomes, phosphatidylcholine and phosphatidylaminoethanol account for about 80% of the total lipids, whereas their content in myelin is only 25%. Cardiolipin has been detected only in mitochondrial membranes. However, the cholesterol content of myelin is much higher than that of the membranes of mitochondria and microsomes. In the case of liver mitochondria and microsomes, it corresponds to *ca.* 5% of the total lipids[78]. Bacterial membranes contain little or no cholesterol. Cholesterol can be incorporated into the cell membrane of *Mycoplasma laidlawii* if it is provided in the culture medium. Data on the lysophosphatide content of the membranes should be regarded with caution, since the results may be influenced by autolysis.

Table 2. Lipid and fatty acid composition of an "average erythrocyte" (mammal).

Compound	Amount	
Lipids:		
Cholesterol	27%	
Phospholipids	60%	
Phosphatidylcholine		31%
Phosphatidylaminoethanol		27%
Phosphatidylserine		12%
Phosphatidylinositol		3%
Phosphatidic acid		2%
Sphingomyelin		25%
Gangliosides	6.5%	
Other glycolipids (sulfatides, cerebrosides)	6.5%	
Fatty acids:		
Palmitic acid	30%	
Stearic acid	16%	
Oleic acid	17%	
Linoleic acid	10.5%	
Arachidonic acid	10%	
Other fatty acids	16.5%	

The lipid composition of erythrocytes depends on the species[79]. It is illustrated in Table 2 for an "average erythrocyte". The most abundant lipid is cholesterol, and this is followed by the group of phospholipids. The phosphatidylcholine content of erythrocytes varies considerably from species to species. It is scarcely detectable in sheep erythrocytes, while its value in pig erythrocytes is 25% and in rat erythrocytes 50%. Glycolipids seem to occur exclusively in plasma membranes. Even within the classes of lipids, the fatty acid composition varies, and the fatty acid pattern of biological membranes fluctuates over a wide range. It also depends on the temperature and the diet[80]. In human erythrocytes, five fatty acids make up more than $^3/_4$ of the total fatty acid content.

Interesting recent observations indicate that lipids are involved in syntheses. Thus a lipid fulfils a catalytic function in the biosynthesis of the peptidoglycan of the bacterial cell wall[81].

4.3. Water

Little attention has been paid so far to water as a membrane component, and the literature data are scanty. Water, which constitutes about 30—50% of the membrane volume, is essential for a number of membrane functions, such as ion permeability and associated electrical phenomena[82,83]. Since little is known about the role of water either in synthetic or in biological membranes, it has been disregarded in most membrane models. However, it must have an influence on other membrane components.

4.4. Ribonucleic Acids

RNA has been detected in several bacterial membranes. The maximum RNA content in liver cell membranes is around 10 μg/mg of protein[49]. RNA has also been found in other animal membrane fractions, though adsorption of RNA on the membranes during preparation cannot be entirely ruled out.

4.5. Carbohydrates

The carbohydrates present in the membrane are bound either to lipids (glycolipids) or to proteins (glycoproteins). The glycoproteins are localized mainly in the outer layer of the plasma membrane.

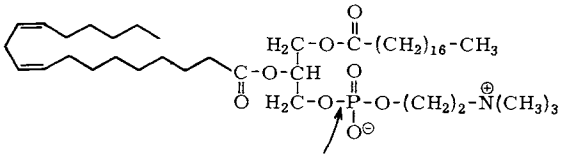
5. Interactions between the Membrane Components

The fact that membranes can be isolated shows that they are stable structures, and do not collapse like a lipid film when removed from their natural environment. Investigations with organic solvents and with mild detergents indicate that covalent bonds between lipids and proteins are of no importance. On the contrary, stabilization appears to be due to ionic bonds, hydrogen bonds, London-van der Waals forces, and hydrophobic bonds.

Phosphatidylcholine (α-lecithin) may be taken as an example of the structure of membrane lipids. Phosphatidylcholines from liver mitochondria and from the endoplasmic reticulum have approximately the same fatty acid composition[80]. Close packing of the molecules within the

[*] The inner and outer mitochondrial membranes differ in their composition. The composition of myelin depends on the state of maturity.

membrane is possible in the physiological pH range. In erythrocyte membranes, the removal of the polar groups of the phospholipids by phospholipase C (the arrow points to the cleavage site) does not lead to breakdown of the membrane structure, so that ionic bonds between proteins and lipids cannot be entirely responsible for stabilizing the structure[84].



According to the "unit membrane" concept, the proteins should be spread on a central bimolecular lipid film. The β-conformation of the membrane proteins should allow closer contact, and hence stronger interactions, between protein and lipid. However, the absence of the IR band at 1630 cm^{-1} indicates the absence of proteins with the pleated sheet structure. Optical rotatory dispersion and circular dichroism studies indicate, on the contrary, that the membrane proteins probably have a globular structure and a high content of α-helix[16,85–88].

The hydrophobic character of many membrane proteins is shown by their poor water-solubility and their solubility in organic solvents. Since these membrane proteins do not differ in any obvious respect from water-soluble proteins in their amino acid compositions, their lipophilic nature can hardly be due to the primary structure, but must result from higher structures such as the α-helix[89]. NMR studies on erythrocyte membranes have shown that the signals of the methylene protons of the hydrocarbon chains in the membranes are strongly influenced by proteins[90,91], probably as a result of hydrophobic bonds between the two components. In the case of phosphatidylcholine, the signals of the paraffin chains disappear from the NMR spectrum on addition of cholesterol. The mobility of the chains appears to be restricted[92]. Differential calorimetric studies on mixtures of phosphatidylcholine and cholesterol have further confirmed this assumption[19].

6. Myelin Figures (Liposomes)

When hygroscopic phospholipids such as phosphatidylcholine come into contact with water, tubular or spherical bodies known as myelin figures (and special forms as liposomes) are spontaneously produced. The physicochemical properties of the phospholipids have been discussed in detail by a number of authors[93,94]. The formation of myelin figures depends on the method, the species of phospholipid, and the temperature. The paraffin chains melt above a critical temperature, and this results in the coexistence of crystalline order of the polar groups and a more disordered liquid phase of the paraffin chains (mesophase). The lipids are in a liquid-crystalline state. The critical temperature is low in the case of phospholipids with short-chain unsaturated fatty acids. Myelin figures are therefore formed at room temperature only by phospholipids that pass into a liquid-crystalline phase at low temperatures. Phospholipids with long-chain saturated hydrocarbons cannot form myelin figures at 25 °C; this becomes possible only when the temperature is raised.

The myelin figures can be recognized under the optical microscope as coiled or layered structures. They are birefringent. Electron-microscopic investigations have shown that they consist of a series of bimolecular lipid layers, which show no tendency to coalesce (Fig. 3). Water is intercalated between the lipid lamellas, and the thickness of the lamellas varies between 80 and 120 Å, depending on the water content. In some cases, very homogeneous structures with a molecular weight of a few million appear,

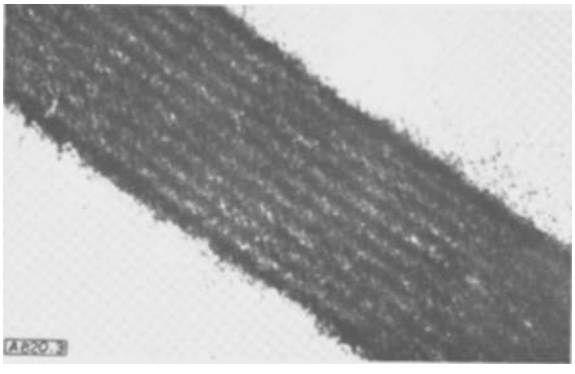


Fig. 3. Electron micrograph of myelin figures from phospholipids after fixation with osmium tetroxide (taken from [95]). Magnification: 825000 ×.

while in others the figures are heterogeneous and the diameters of the cylinders differ. A relatively stable phospholipid dispersion in which the liposomes are roughly equal in size can be obtained by ultrasonic treatment.

Their structure and behavior make liposomes suitable for use as models of biological membranes; several research groups[96–100] have carried out extensive studies on these particles. Since the liposomes enclose water during their formation, they can be used for permeability studies. Efflux experiments with anions and cations have shown that sufficiently small liposomes have no pores; anions and cations permeate at different rates. Observations made on synthetic membranes of identical or similar chemical composition have added to the picture of the permeability properties[101,102].

After fixation with OsO_4, myelin figures exhibit a trilaminar structure similar to that of biological membranes. This trilaminar structure is even more pronounced after addition of proteins to the lipid lamellas. It is often assumed that the hydrophilic groups of the phospholipids are oriented outward in the bimolecular film, while the hydrocarbon chains of both layers of molecules are turned inwards, but it is possible that the orientation of the molecules is exactly the opposite. This question cannot be answered by an electron micrograph alone.

7. Membrane Models

In 1935, *Danielli* and *Davson*[28] proposed a membrane model based mainly on the results of functional and physicochemical studies on plasma membranes. This model is

shown in Fig. 4a. A central lipid layer is separated on both sides from the water-filled compartments, the intracellular space and the surrounding medium, by protein layers. These views of *Danielli* and *Davson* determined the picture of the ultrastructure of biological membranes for a number of years.

This model was modified in three points by *Robertson*[44, 45], mainly on the basis of electron-microscopic evidence. The number of lipid layers was limited to two; instead of being globular, the proteins were assumed to be spread on the lipid layer, and the membrane was assumed to have an asymmetric structure. *Robertson* also suggested that this concept was generally valid ("unit membrane"). These views are illustrated schematically in Fig. 4b. In the center

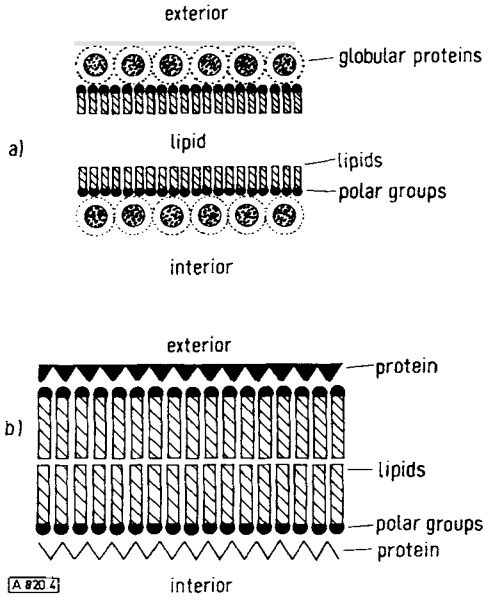


Fig. 4. Membrane models (after [29]).
(a) Danielli-Davson membrane model;
(b) *Robertson*'s membrane model ("unit membrane"). The proteins are in the β-conformation and are different from one another.

is the lipid film, about 50 Å thick, which consists of two layers of molecules. The hydrophobic parts of the molecules are turned toward the inside of the membrane, while the hydrophilic groups are directed outward, and form bonds with the spread proteins.

According to recent investigations, however, the β-conformation of the proteins no longer appears to be tenable. It was also difficult to reconcile several observations with *Robertson*'s concept. Thus, thickness determinations on various membranes showed considerable differences. The typical trilaminar picture could be obtained even for mitochondrial membranes whose lipids had been removed by extraction. The membranes do not collapse despite the extraction of the lipids. It appeared that the rapid restoration of the membrane after lesions could be readily explained by the incorporation of preformed structural elements as subunits. Electron-microscopic plan views of biological membranes often show structuring that suggests that they are built up from subunits.

Results that initially seemed convincing were thus collected. However, a number of arguments have not been able fully to stand up to critical reexamination. The extractions of lipids from the mitochondrial membranes were incomplete. Protein bridges could penetrate the lipid layer and connect the two protein layers, with the result that the collapse of the membrane is prevented. The structure made up from subunits as seen in the electron micrograph could be confined to the protein layer, or it could be an artefact. The "unit

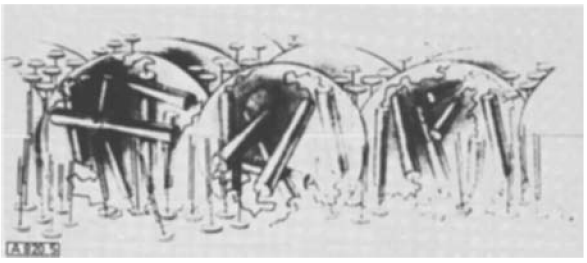


Fig. 5. Membrane model proposed by *Sjöstrand* (p. 10 of [48]) to explain electron-microscopic findings for cytoplasmic membranes. Construction of the membrane from globular proteins, between which the lipids are interposed.

membrane" model has recently been opposed by "subunit" models, according to which the membrane structure can be described as a two-dimensional aggregate of lipoprotein subunits[48, 88, 89, 103, 104]. To illustrate this type of approach, *Sjöstrand*'s membrane model[48] is shown in Fig. 5.

The answers to the questions which of the models is preferable and what modifications are necessary will have to await the outcome of further investigations.

8. Functions of Biological Membranes

8.1. Membranes as Barriers and Pumps

Membranes on the one hand are permeability barriers between two spaces, and on the other they must allow the passage of substances between these spaces in both directions. Thus the plasma membrane must not be equally permeable to all substances, but must be able to select among the substances offered to it for passage. The passage of some substances through the membrane is hindered, while that of others is facilitated. According to the "unit membrane" concept, the osmotic barrier for hydrophilic substances is the quasi-liquid lipid phase in the interior of the membrane. The greater ease of penetration of lipophilic substances has already been mentioned.

In the use of Fick's law to describe the *diffusion* of particles through biological membranes, difficulty is encountered in the determination of the diffusion constant[*]. This led to the use of another parameter, the diffusion coefficient, to describe the diffusion. Some substances passed through the membrane much more rapidly than one would expect in the case of diffusion. In these cases, the rate of entry of a substance tends toward a maximum with increasing concentration *(facilitated diffusion, active transport)*[112]. Since the investigations by *Osterhout*[105], it is usually assumed that mobile carriers within the membrane are responsible for translocations of this nature. The essential features of

[*] The diffusion distance and the concentration profile are not accurately known for biological membranes.

the transport are structure specificity, ability to be inhibited and activated, and saturation behavior[30, 106-111].

Absorption and secretion in metazoa are the responsibility of highly specialized cells such as those of the intestinal or renal epithelia. High molecular weight compounds or particles can pass through the membrane by pinocytosis or phagocytosis.

8.2. Conduction of Stimuli

Biological membranes can be stimulated by electrical, mechanical, chemical, and thermal stimuli. The stimulation is associated with electrical phenomena that occur as a result of the movement of ions (K^+, Na^+, and Cl^-) through the membrane. This involves localized changes in the permeability of the membrane. K^+, Na^+, and Cl^- are unevenly distributed in the intracellular and extracellular spaces. This uneven distribution is probably due to the difference in the concentrations of macromolecular polyelectrolytes on the two sides of the membrane (Donnan distribution) and essentially to the ion pumps. Membrane-bound adenosine triphosphatases that can be stimulated by Na^+ and K^+ are evidently involved in the active transport of ions[113].

The potentials that arise on porous membranes as a result of the different penetration rates of the ions can be described by the Nernst equation or, if the salt concentration on both sides of the membrane is the same, by Planck's formula. *Hodgkin* and *Katz*[114] have published a formula for the determination of the resting potential of biological membranes in which the permeability coefficients of $K^+ : Na^+ : Cl^-$ are assumed to be related as 1 : 0.04 : 0.45. At the instant of stimulation, a radical change occurs in the permeability of the membrane, and the ratio of the permeability constants can now be expressed as 1 : 20 : 0.45. The action potential can thus be attributed to an extreme increase in the sodium permeability.

8.3. Membranes as Receptors

The membranes are the sites of action of many hormones that influence the permeability or act on the membrane enzymes. The membrane enzymes then liberate a transmitter substance (second messenger), which intervenes in the metabolism. The surface structures of the cells play a decisive role in immunochemistry. The contact inhibition of growing cells must also be initiated by the cell membrane. This contact inhibition is lacking in tumor cells[115].

8.4. Membranes as Enzyme Supports

Reference has already been made to the large number of membrane-bound enzymes. Thus the components of the respiratory chain are bound to the mitochondrial membrane, and a high degree of order is achieved in the sequence in this way. Protein synthesis in animal cells takes place on the membranes of the endoplasmic reticulum, and on the plasma membrane in bacteria. The division of the cell into reaction spaces (compartments) by membranes ensures that many metabolic sequences can proceed undisturbed.

8.5. Membranes as Protection

The plasma membrane protects the cell when its environmental conditions change. By exclusion or neutralization of certain substances, interference with intracellular biochemical reactions is avoided. Enzymes that are dangerous to the cells are enclosed by membranes (in *e.g.* lysosomes) and withheld from their substrates in this way. Many additions could be made to the list, but the functional versatility of membranous structures is clear from the points mentioned.

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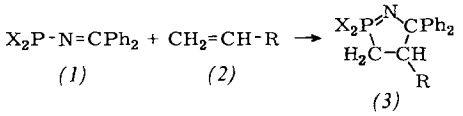
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A Novel Type of 1,3-Dipolar Cycloaddition: 1,2-Aza-P^{V}-phosphol-1-ines from Methyleneaminophosphanes[1]

By *Alfred Schmidpeter* and *Werner Zeiss*[*]

Dedicated to Professor Egon Wiberg on the occasion of his 70th birthday

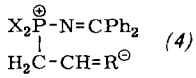
The recently synthesized methyleneaminophosphanes *(1)*[2] react with electrophilic olefins *(2)* such as acrylonitrile and methyl acrylate to give stable 1:1 adducts. The products are crystalline and, unlike the readily soluble yellow starting compounds *(1)*, are colorless and relatively sparingly soluble. It follows from the characteristic J_{PCH} and J_{PCCH} values of the ^{1}H-NMR spectra that the olefin *(2)* is bound *via* its methylene group to the phosphorus of *(1)*, and from the non-equivalence of the two methylene protons that the formerly olefinic bond does not rotate in the adduct; furthermore, the X residues bound to the phosphorus are also non-equivalent. Thus, the spectra confirm a cyclic structure *(3)*.



(1) + *(2)* → *(3)*

The 1,2-aza-P^{V}-phosphol-1-ines *(3)* are the first cyclic phosphazenes having less than six members in the ring; the five-membered ring phosphazenes prepared previously do not exist as such, but as tricyclic dimers[3,4].

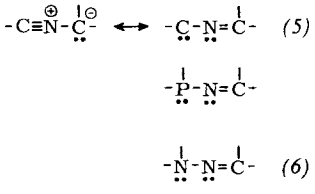
The possibility of these compounds being open-chain betaines *(4)* can be ruled out. Only doubly activated olefins such as dicyanoethylene, but not the olefins used here, yield stable betaines on reaction with triaryl- or trialkylphosphanes. Moreover, for a betaine structure *(4)* to be plausible the two X-residues and the two methylene protons of the central X_2PCH_2 group respectively would have to be equivalent.



(4)

However, *(4)* must be considered as a possible intermediate in the cycloaddition.

The reaction under discussion is a 1,3-dipolar cycloaddition and, as a consequence, compounds *(1)* represent a novel type of 1,3-dipoles with dominating nucleophilic character. The dichloromethyleneaminophosphane *(1)*, X = Cl, does not react with the dipolarophiles used here. As 1,3-dipoles, the methyleneaminophosphanes are unique in that the "uncharged" and "all-octet" canonical forms coincide. In some ways they are to be compared with the nitrile ylides *(5)*; as in many other cases X_2P— can to a certain extent replace XC—.



(5)

(6)

Equalization between nucleophilic and electrophilic ends of the dipoles in the cycloaddition of methyleneamino-

Table. NMR data of azaphospholines *(3)*. The chemical shifts are referred to H_3PO_4 (external) and TMS (internal) and are quoted negatively towards low field.

Cis and *trans* indicate the position with respect to the proton on C–4. Assignment of the signals of the two methyl protons was based on the assumption that $J_{HCCH\,cis} > J_{HCCH\,trans}$ [5]. Only the two intense transitions of the AB spectrum were found in the two cases of particularly small shift differences between *cis* and *trans* methylene protons; the quoted δ-values are calculated on the assumption that $J_{HCH} = 15 \pm 1$ Hz. Assignment of signals for the X-methyl protons was not possible; corresponding δ- and *J*-values are correlated in the table.

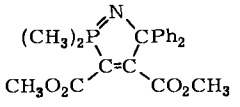
X		C_6H_5	C_6H_5	CH_3	CH_3	OCH_3	OCH_3	
R		CN	CO_2CH_3	CN	CO_2CH_3	CN	CO_2CH_3	
$\delta^{31}P \cdot 10^6$		−48.2			−40.1	−75.0	−75.9	
$\delta^1H \cdot 10^6$								Signal splitting
$CH_3(X)$				−1.26	−1.08	−3.40	−3.20	A-part, A_3X
				−1.67	−1.60	−3.82	−3.82	A-part, A_3X
CH_2	*cis*	−2.88	−2.78	−2.30	−2.04	−2.33	−2.02	A-part }
	trans	−2.93	−3.02	−2.54	−2.43	−2.40	−2.29	B-part } ABMX
CH		−4.27	−4.33	−4.22	−4.18	−4.18	−4.28	M-part }
$CH_3(R)$			−2.98		−3.02		−2.98	
J(Hz)								
PCH_3				13.0	12.9			
				13.5	13.9			
$POCH_3$						11.9	11.8	
						12.0	11.5	
PCH_2	*cis*	7.5	8.1	8.0	8.6	6.5	14.1	
	trans	7.5	8.2	6.1	6.6	5.2	14.6	
PCCH		18.9	19.3	21.3	23.1	23.4	24.6	
HCH			14.9	15.3	14.7		15.5	
$HCCH_2$	*cis*	6.0	7.3	6.7	7.3	6.5	7.8	
	trans	5.6	4.0	3.5	1.9	5.2	3.5	

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phosphanes is rendered possible by the formation of a phosphazene-(pd) π bond. It certainly remains weaker than *via* a (pp)π bond. This possibility, and consequently also the dipolar activity are completely lacking in the case of the homologous hydrazones *(6)*, unless the betaine charges being formed can be eliminated by a secondary reaction.

Acetylenedicarboxylates also react as dipolarophiles with methyleneaminophosphanes to give 5*H*-1,2-aza-P^{v}-pho^{v}-pholes:

$$(CH_3)_2P\text{-}N{=}CPh_2 + CH_3O_2C\text{-}C{\equiv}C\text{-}CO_2CH_3 \rightarrow$$



(7)

Compound *(7)* is symmetrical in regards to the plane of the ring and consequently gives a simple ^{1}H-NMR spectrum: a doublet for the equivalent P methyl groups (δ^1H -1.74×10^{-6}; $J_{PCH}=13.9$ Hz) and two singlets for the ester methyl protons (δ^1H -3.80 and -3.54×10^{-6}).

Experimental:

A solution of the dimethyl- or diphenyldiphenylmethyleneaminophosphane *(1)*, X = CH_3, C_6H_5, in ether or methylene chloride is stirred for about 20h at room temperature with an equimolar amount of the dipolarophile.

Dimethoxydiphenylmethyleneaminophosphane *(1)*, X = OCH_3, is heated together with the dipolarophile in the absence of solvent at 50 °C for a short time or in acetonitrile under reflux for 2h. The product crystallizes either spontaneously or on addition of ether and is analytically pure after washing with ether.

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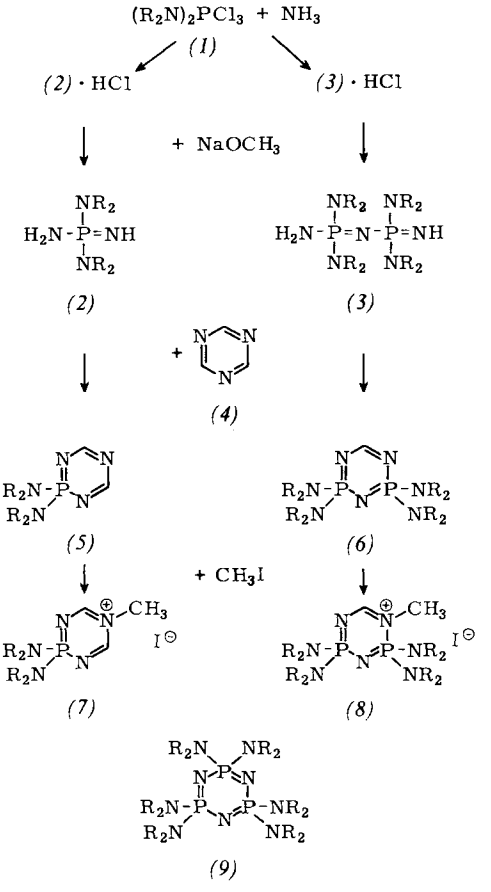
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1,3,5-Triaza-phosphorines and -diphosphorines from 1,3,5-Triazine[1]

By *Alfred Schmidpeter* and *Caspar Weingand*[*]

Dedicated to Professor Egon Wiberg on the occasion of his 70th birthday

Ammonolysis of trichlorobis(dialkylamino)phosphoranes *(1)* affords the hydrochlorides of aminophosphazenes *(2)* and aminodiphosphazenes *(3)*, from which the free bases can be liberated[2]. Mild ammonolysis does not lead to (complete) condensation to cyclooligophosphazenes $[(R_2N)_2PN]_n$. However, compounds *(2)* and *(3)* can be considered as open-chain elements of the cyclophosphazene structure that have been terminated by added NH_3. In this sense together with another suitable structural unit they permit the condensation to be completed by elimination of ammonia with formation of heterocycles. Thus warming *(2)* or *(3)* with a stoichiometric amount of *s*-triazine yields 2,2-bis(dialkylamino)-1,3,5,2-triazaphosphorines *(5)* or 2,2,4,4-tetrakis(dialkylamino)-1,3,5,2,4-triazadiphosphorines *(6)*, respectively.



(9)

These products form a bridge between *s*-triazine *(4)* and the cyclotriphosphazenes *(9)*, and both contain two types of nitrogen ring members that are differentiated by being flanked by either one or two carbon or phosphorus atoms. Treating *(5)* or *(6)* with methyl iodide methylates exclusively a ring nitrogen atom—not the exocyclic nitrogen. Even with this limitation two methylated products are possible, but there is selective formation of 5-methyl-1,3,5,2-triazaphosphorinium iodide *(7)* (in which the symmetry of the starting material is preserved) and 1-methyl-1,3,5,2,4-triazadiphosphorinium iodide *(8)* (in which the symmetry is destroyed) (cf. Table 1). Thus the nitrogen atom with the fewer phosphorus neighbors is always the more nucleophilic[3]:

$$\text{-}\overset{|}{P}{=}N\text{-}\overset{|}{P}{=} < \text{-}\overset{|}{P}{=}N\text{-}\overset{|}{C}{=} < \text{-}\overset{|}{C}{=}N\text{-}\overset{|}{C}{=}$$

This is in accord with the results obtained on protonation and alkylation of other triazadiphosphorines[4], but it was not be expected from comparison of the basicities of the ring nitrogen atoms of the end members of the series: *s*-triazines are very weak bases[5], whereas pK values of 7.5 to 8.5 were found for compounds *(9)*[6].

The chemical shifts for the C and P ring members of *(5)* and *(6)* are remarkably close to, although always at

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Table 1. NMR spectra of compounds *(5)* to *(8)* [a]. Chemical shifts δ^1H, $\delta^{13}C$, and $\delta^{31}P$ are in ppm with reference, respectively, to TMS (internal), benzene (external), or H_3PO_4 (external). Values at lower field are given as negative. $\delta^{13}C$ was measured with $(CD_3)_2C^*O$ as external standard and calculated by subtraction of 77.0 ppm. Coupling constants J are in Hz. Values in parentheses are signal multiplicities, m indicating an unresolved multiplet.

	R		$\delta^{31}P$	—CH= $\delta^{13}C$	J_{PNC}	—CH= δ^1H	J_{PNCH}	R_2N— $\delta^{13}C$	δ^1H_α	J_{PNCH}	$\delta^1H_{\beta-\delta}$	J_{HCCH}	H_3C—N< δ^1H	J_{PNCH}
(5)	C_2H_5	undiluted	−27.9			−7.93 (2)	39.5		−3.07 (2 × 4)	11.9	−1.10 (3)	7.1		
(5)	*n*-C_4H_9	in CH_2Cl_2	−26.7	−40.8 (2)	10.0	−7.95 (2)	39.6	+ 84.5 + 98.2 +109.1	−2.95 (m)	*ca.* 11	−1.95 to −0.47 (m)			
(6)	CH_3	undiluted	−27.7	−42.4 (3)	5.5	−7.82 (2)	47.4	+ 95.7	−2.57 (2)	11.2				
(7)	C_2H_5	in CH_2Cl_2	−17.1			−8.63 (2)	36.6		−3.18 (2 × 4)	12.8	−1.17 (3)	7.1	−3.90 (1)	7.2
(8)	CH_3	in CH_2Cl_2 *o* [b]	−25.8			−8.25 (2 × 2)	22.0		−2.86 (2)	11.4			−3.37 (2)	
		p	−18.3				49.2		−2.73 (3)	11.2				

[a] Work performed together with *Klaus Schumann*.
[b] *o* and *p* denote *ortho*- and *para*-position, respectively, to the methylated nitrogen atom.

somewhat lower field[7] than, those of the symmetric compounds *(4)*, $\delta^{13}C = -39.0 \times 10^{-6}$[8] and *(9)*, R = CH_3, $\delta^{31}P = -25 \times 10^{-6}$[9]. On the other hand, the chemical shifts of the ring methine protons of *(5)* and *(6)* have moved to higher field by 1.3 and 1.4 ppm, respectively, in comparison with that of *(4)* $\delta^1H = -9.25 \times 10^{-6}$[10]. This can be interpreted as a considerable weakening of the magnetic anisotropy of the triazine ring caused by inclusion of $P(NR_2)_2$ as a ring member in place of CH; inclusion of a second $P(NR_2)_2$ ring member makes, however, little difference to this. In comparison, benzene protons are shifted by *ca.* −1.6 ppm by the anisotropy of the ring. A large endocyclic PNCH coupling[11] is characteristic for all the compounds described here; the value for *(8)* is the largest $^3J_{PH}$ value ever reported.

2,2-Bis(dialkylamino)-1,3,5,2-triazaphosphorines and 2,2,4,4-tetrakis(dialkylamino)-1,3,5,2,4-triazadiphosphorines

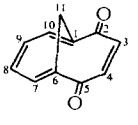
A benzene solution of an aminophosphazene *(2)* or aminodiphosphazene *(3)* is treated with two-thirds or one-third, respectively, of the equimolar amount of *s*-triazine. When the mixture is heated to the boiling point ammonia is evolved and the triazine dissolves. After 3–4 h the benzene is distilled off and the residue is then distilled at 1 torr and a bath-temperature of 120 °C (R = CH_3 or C_2H_5) or is chromatographed (R = *n*-C_4H_9) in CH_2Cl_2 on Al_2O_3. The products are colorless liquids and analytically pure and are obtained in yields of 70–90%.

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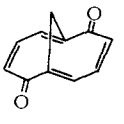
Dicarbonyl Derivatives of 1,6-Bridged [10]Annulenes

By *Emanuel Vogel, Elmar Lohmar, Walter A. Böll, Bernd Söhngen, Klaus Müllen, and Harald Günther*[*]

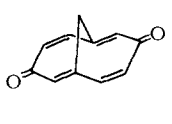
For a systematic comparison of bridged [10]annulenes[1] with the classical aromatic compounds benzene and naphthalene it would be of considerable interest to clarify the problem of whether dicarbonyl derivatives of 1,6-methano[10]annulene *(4)* are to be regarded as "quinones". It can easily be seen that the same number and same types of "quinones" can be derived from *(4)* as from naphthalene. Bicyclo[4.4.1]undeca-3,6,8,10-tetraene-2,5-dione *(1)*, bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,7-dione *(2)*[2], and bicyclo[4.4.1]undeca-1,4,6,9-tetraene-3,8-dione *(3)* may be named as representative members. We here report attempted synthesis of the compound *(1)*.



(1)

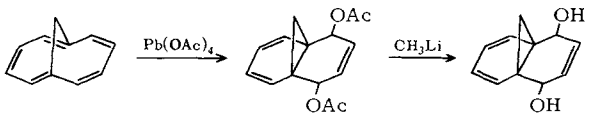


(2)

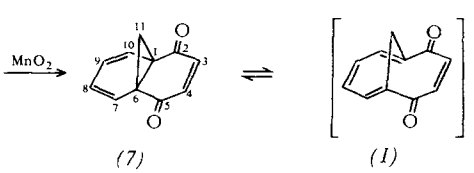


(3)

On treatment with lead tetraacetate in glacial acetic acid at 60–80 °C, 1,6-methano[10]annulene *(4)* affords the *cis*-1,4-diacetate *(5)*, m.p. 145–147 °C, in 30% yield with high stereoselectivity. The presence of the norcaradiene structural moiety in *(5)* and the *cis*-configuration of the acetate groups follow compellingly from the ^1H-NMR spectrum [(in $[D_6]$benzene) AA'BB' system, centered at $\tau = 3.9$ (4H); singlets at 4.38 (2H), 4.61 (2H), and 8.27 (6H); AB system at 7.48 and 9.82 with $J = 6.2$ Hz (2H); $J(^{13}C—H)$



(4) *(5)* *(6)*



(7) *(1)*

[*] Prof. Dr. E. Vogel, Dr. E. Lohmar, Dr. W.A. Böll, Dipl.-Chem. B. Söhngen, Dipl.-Chem. K. Müllen, and Prof. Dr. H. Günther
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of the proton at highest field: 159 Hz]. The configuration of the acetate groups in relation to the cyclopropane ring still remains to be clarified. When the diacetate was treated with ethereal methyllithium at −50 °C, a diol of m.p. 151–152 °C (yield 74%) was formed which, according to the NMR spectrum has structure *(6)*. The diol *(6)* can be converted by manganese dioxide in benzene almost quantitatively into a yellow dicarbonyl compound, m.p. 107–108 °C, which is stable in absence of light and oxygen and to which the norcaradiene structure *(7)* must be assigned unambiguously on the basis of spectral findings.

The NMR spectrum of the dicarbonyl compound (in [D_6]acetone) shows an AA'BB' system (H^7—H^{10}) centered at $\tau = 3.52$, a singlet at 3.49 (H^3, H^4), and an AB system at 7.41 (*anti*-H^{11})[3] and 9.22 (*syn*-H^{11}) with $J = 4.1$ Hz. The coupling constants of the olefinic protons H^7—H^{10}[4] (see Table 1), on the one hand, and the geminal coupling of the CH_2 protons on the other provide a decisive argument in favor of structure *(7)*. The electron spectrum [(in methanol), $\lambda_{max} = 226$ ($\varepsilon = 15400$), 271 (2240), 324 (248), 405 nm (186)] also supports the structure *(7)*; the IR spectrum, with a broad carbonyl band at 1665 cm^{-1} (in KBr) is not very revealing.

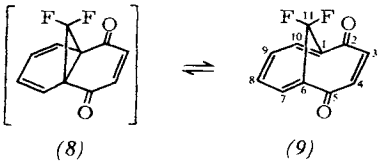
Table 1. Chemical shifts (τ values in ppm) and H,H coupling constants (Hz) of the olefinic protons in *(7)* and *(9)*.

	H^7, H^{10}	H^8, H^9	H^3, H^4	$J_{7,8} = J_{9,10}$	$J_{8,9}$	$J_{7,9} = J_{8,10}$	$J_{7,10}$
(7)	3.25 [a]	3.88 [a]	3.49	9.75	6.03	0.83	1.21
(9)	2.82	2.44	3.38	6.74	10.59	0.12	1.34

[a] The assignment of H^7, H^{10}, and of H^8, H^9, respectively, is uncertain.

The replacement of the two methylene protons in *(7)* by fluorine offers the possibility of shifting the position of the equilibrium between the norcaradiene and the cycloheptatriene tautomer in favor of the latter [*(7)*⇌*(1)* *versus* *(8)*⇌*(9)*], for, as the thermal behavior of perfluorocyclopropanes shows, ring strain is considerably increased by geminal fluorine substituents[5].

11,11-Difluoro-1,6-methano[10]annulene[6] reacts with lead tetraacetate in glacial acetic acid in the same way as *(4)*, although less readily (reflux), yielding a symmetrical *cis*-1,4-diacetate (m.p. 171–172 °C; yield 10%). The ^{1}H-NMR spectrum of the compound confirms the expectation that in this case we are dealing with a cycloheptatriene derivative, and the same applies to the diol [m.p. 175–176 °C (several recrystallizations from ethyl acetate); crude yield 78%] obtained from the diacetate by means of methyllithium at −50 °C. Finally, oxidation of the crude diol with manganese dioxide in acetone afforded the desired 11,11-difluorobicyclo[4.4.1]undeca-3,6,8,10-tetraene-2,5-dione *(9)* as a light-sensitive yellow compound of m.p. 119–120 °C (yield 50%).



(8) *(9)*

Structure *(9)* was proved by the NMR spectra. The ^{1}H-NMR spectrum ([D_6]-acetone) contained an AA'BB' system (H^7—H^{10}) disturbed by H, F coupling and centered at $\tau = 2.62$, as well as a singlet at 3.38 (H^3, H^4), whereas the ^{19}F-NMR spectrum [($CDCl_3$); CCl_3F as external standard] contained an AB system at 103.5 and 110.8 ppm with $J = 238$ Hz. The presence of a cycloheptatriene is convincingly shown by the coupling constants of the olefinic protons H^7—H^{10} (see Table 1) and by the absorption of these protons at relatively low field strength[7]. Furthermore, the ^{19}F-NMR parameters point to this type of structure, for if the CF_2 group were part of a cyclopropane ring the fluorine atoms should not only absorb at higher field strengths but also should show smaller geminal coupling[8–10].

The electron spectrum of the compound [(in methanol) $\lambda_{max} = 210$ ($\varepsilon = 27900$), 236 (15350), 245 (15100, sh), 318 (2600), 398 (325), 415 nm (300)] indicates, in accord with structure *(9)*, stronger conjugation than in the norcaradiene *(7)*. The IR carbonyl absorption [relatively sharp band at 1658 cm^{-1} (in KBr)] corresponds, as does that of *(7)*, to that of an α,β-unsaturated ketone or of a quinone[11].

Chemical and physicochemical studies of *(7)* and *(9)* are in progress to provide further information about the quinonoid nature of these dicarbonyl compounds.

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[1] Reviews: a) *E. Vogel* in: Aromaticity, Special Publication No. *21*, Chem. Soc., London 1967, p. 113; b) *E. Vogel*, Chimia *22*, 21 (1968); c) *E. Vogel*, Proc. Robert A. Welch Foundation Conferences on Chemical Research, XII. Organic Synthesis, Houston, Texas, 1968, p. 215.

[2] For synthesis of *(2)* see *E. Vogel, W. A. Böll*, and *E. Lohmar*, Angew. Chem. *83*, 403 (1971); Angew. Chem. internat. Edit. *10*, 399 (1971).

[3] *syn* and *anti* refer to the diene part of the molecule.

[4] *H. Günther* and *H.-H. Hinrichs*, Liebigs Ann. Chem. *706*, 1 (1967).

[5] *R. A. Mitsch* and *E. W. Neuvar*, J. Phys. Chem. *70*, 546 (1966); see also *H. Günther*, Tetrahedron Lett. *1970*, 5173.

[6] *V. Rautenstrauch, H.-J. Scholl*, and *E. Vogel*, Angew. Chem. *80*, 278 (1968); Angew. Chem. internat. Edit. *7*, 288 (1968).

[7] The position of the AA'BB' system of the protons H^7—H^{10} reflects strong conjugation between the two halves of the molecule, such as is present only in the cycloheptatriene structure.

[8] References for ^{19}F-NMR parameters of *gem*-difluorocyclopropanes: a) *R. A. Mitsch*, J. Amer. Chem. Soc. *87*, 758 (1965); b) *W. D. Phillips*, J. Chem. Phys. *25*, 949 (1956).

[9] The spectral data for *(7)* and *(9)* do not exclude the possibility that these compounds exist in rapidly established equilibrium with their cycloheptatriene or norcaradiene tautomers [*(1)* and *(8)* respectively]; the concentrations of tautomers *(1)* and *(8)*, however, should not exceed 20%. If more than *ca.* 5% of *(1)* and *(8)* were present, the NMR spectra should be temperature-dependent (measurements are in progress).

[10] We thank Dr. *P. Junkes* for determination of the ^{19}F-NMR spectra.

[11] With potassium *tert*-butoxide in dimethyl sulfoxide, the tricyclic dicarbonyl compound *(7)* affords a semiquinone which, according to its ESR spectrum, has a bicyclic structure: *G. A. Russell, T. Ku*, and *J. Lokensgard*, J. Amer. Chem. Soc. *92*, 3833 (1970).

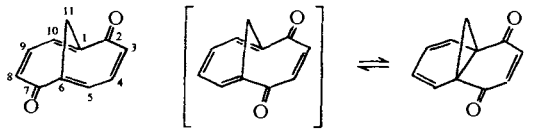
Bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,7-dione

By *Emanuel Vogel, Walter A. Böll*, and *Elmar Lohmar*[*]

Bicyclo[4.4.1]undeca-3,6,8,10-tetraene-2,5-dione *(2)*, a diketo derivative of 1,6-methano[10]annulene corresponding to *p*-benzoquinone or 1,4-naphthoquinone, defies attempts at synthesis because, contrary to expectation, it has a

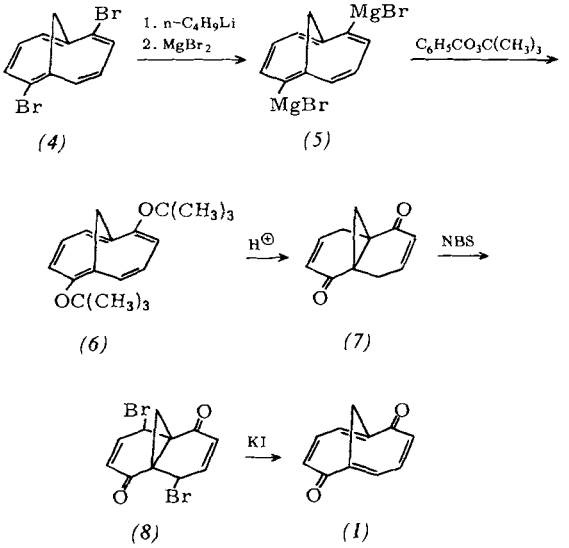
[*] Prof. Dr. E. Vogel, Dr. W.A. Böll, and Dr. E. Lohmar
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higher free energy than its valence isomer with the norcaradiene structure *(3)*[1]. With bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,7-dione *(1)*[2], an isomer of *(2)*, a cycloheptatriene-norcaradiene equilibrium is ruled out. Thus only a strong tendency of *(1)* to polymerize should stand in the way of its synthesis.



(1) *(2)* *(3)*

A route to *(1)* was opened by the known 2,7-dibromo-1,6-methano[10]annulene *(4)*[3]. For converting *(4)* into 1,6-methano[10]annulene-2,7-diol or its keto tautomers we used a procedure that had already proved its value for the preparation of 2-hydroxy-1,6-methano[10]annulene from 2-bromo-1,6-methano[10]annulene[4]; in this, the appropriate bromide was converted into the Grignard reagent and this was treated with *tert*-butyl perbenzoate[5], yielding the *tert*-butyl ether which is readily cleaved by acid. The dibromide *(4)* did not, in the event, react with magnesium in the desired manner, but the bifunctional Grignard reagent *(5)* could be obtained by interchange of the metal between the dilithium compound, generated from *(4)* with butyllithium in ether[6], and anhydrous magnesium bromide. When *(5)* was treated with ethereal *tert*-butyl perbenzoate at 0 °C, subsequent chromatography on aluminum oxide followed by distillation afforded the di-*tert*-butyl ether *(6)* as a pale yellow liquid, b.p. 108–110 °C/0.01 torr (yield 50%) [NMR spectrum (in CCl_4): ABC system at $\tau = 2.4$–3.4 (6H) and singlets at 8.69 (18H) and 10.55 (2H)]. Fission of *(6)* effected by a catalytic amount of *p*-toluenesulfonic acid in benzene at 80 °C for 10 min gave a homogeneous colorless substance of composition $C_{11}H_{10}O_2$ and m.p. 138–140 °C (56% yield), which spectra

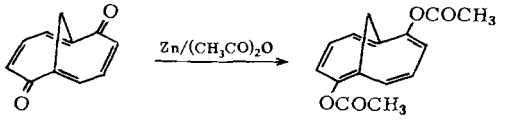


(4) *(5)* *(6)* *(7)* *(8)* *(1)*

showed conclusively to be the diketone *(7)* with cyclopropane structure [NMR (in $CDCl_3$): AB system with triplet splitting of each line at $\tau = 3.1$–4.2 (4H), quartet at 7.0 (4H), and singlet at 8.33 (2H); UV (in cyclohexane): $\lambda_{max} = 214$ ($\varepsilon = 20\,500$), 331 nm (150); IR (in KBr): carbonyl band at 1650 cm^{-1}]. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone did not dehydrogenate *(7)*, so an attempt was made to approach *(1)* by way of the dibromide *(8)*. With two equivalents of *N*-bromosuccinimide (NBS) in boiling carbon tetrachloride, *(7)* gave a crystalline dibromo substitution product (crude yield *ca.* 80%); this was obviously a mixture of the three possible stereoisomeric dibromides *(8)* since the NMR spectrum of this product contained two singlets and an AB system for the cyclopropane protons. Potassium iodide[7] in acetone dehalogenated the dibromide mixture to the desired bicyclo[4.4.1]undeca-3,5,8,10-tetraene-2,7-dione *(1)* which was obtained as yellowish-orange crystals (from acetone), m.p. 147–148 °C (yield *ca.* 50%), after chromatography on silica gel.

Proof of the structure of *(1)* was provided by the NMR spectrum. This showed only an ABC system at $\tau = 3.0$–3.8, assigned to the six vinylic protons, [chemical shifts and coupling constants determined by analysis: $\tau_{3,8} = 3.71$, $\tau_{4,9} = 3.11$, $\tau_{5,10} = 3.75$; $J_{3,4} = 11.52$ Hz, $J_{3,5} = -0.06$ Hz, and $J_{4,5} = 5.22$ Hz (positional numerals as in formula *(1)*)][8] plus a singlet at $\tau = 6.83$ arising from the CH_2-bridge protons, and it thus has the form expected from the C_2 symmetry of *(1)*. Further the UV and IR spectra are in accord with structure *(1)* [λ_{max} (in cyclohexane) = 244 ($\varepsilon = 3750$, sh), 342 (7300), 431 nm (1600); carbonyl or double-bond bands (in KBr) at 1625, 1635, and 1645 cm^{-1}].

The physical and spectroscopic properties determined so far for *(1)* leave it open whether this compound can be described as a quinone. The chemical behavior appears to justify such a description, for treating *(1)* with zinc and acetic anhydride in the presence of pyridine leads readily to reductive acetylation that affords the aromatic



(1) *(9)*

2,7-diacetoxy-1,6-methano[10]annulene *(9)* of m.p. 130–131 °C; this product is identical with that obtained by acid-catalyzed reaction of *(6)* with acetic anhydride.

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[1] *E. Vogel, E. Lohmar, W. A. Böll, B. Söhngen, K. Müllen,* and *H. Günther,* Angew. Chem. *83*, 401 (1971); Angew. Chem. internat. Edit. *10*, 398 (1971).

[2] To the best of our knowledge, the 1,5-naphthoquinone analogous to *(1)* is unknown.

[3] *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 Lett. *1966*, 1569.

[4] *W. A. Böll,* Angew. Chem. *78*, 755 (1966); Angew. Chem. internat. Edit. *5*, 744 (1966); *E. Vogel* and *W. A. Böll,* unpublished work.

[5] *S.-O. Lawesson* and *N. C. Yang,* J. Amer. Chem. Soc. *81*, 4230 (1959).

[6] *E. Vogel* in: Aromaticity, Special Publication No. *21*, Chem. Soc., London 1967, p. 113.

[7] When sodium iodide is used, *(1)* is accompanied by an iodine-containing product, presumably the diiodide corresponding to *(8)*; when kept, this product decomposes to *(1)* in an apparently reversible reaction.

[8] We thank *H. Schmickler* for analysis of the ABC system.

Interaction between the Orbitals of Lone Pair Electrons in Dicarbonyl Compounds[1]

By *Dwaine O. Cowan, Rolf Gleiter, Joseph A. Hashmall, Edgar Heilbronner,* and *Volker Hornung*[*]

As a result of EHT and CNDO/2 calculations *J. R. Swenson* and *R. Hoffmann*[2] prophesied that interaction between the non-bonding orbitals n_1 and n_2 of the two carbonyl groups in a dicarbonyl compound would lead to molecular orbitals with clearly split orbital energies. This should be true even when n_1 and n_2 are widely separated in space. It was shown that the interaction mechanism is mainly of the "through-bond" type[3], in as far as the linear combinations

$$n_+ = (n_1 + n_2)/\sqrt{2}$$
$$n_- = (n_1 - n_2)/\sqrt{2}$$

which differ little in energy as a result of "through-space" interaction, can mix strongly with other σ-orbitals of appropriate symmetry. The orbital diagram of s-*trans*-glyoxal shown in Fig. 1 affords an example of this type of interaction.

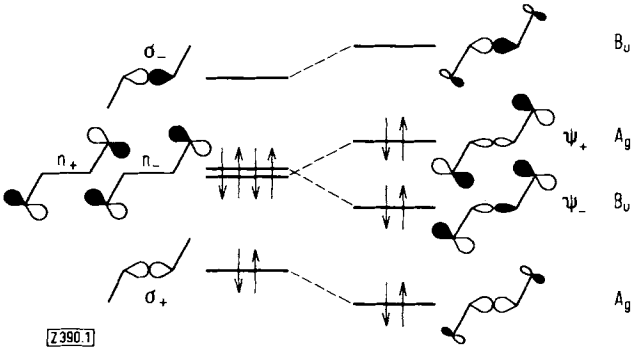


Fig. 1. Schematic orbital diagram of the "through-bond" interaction between the linear combinations n_+ and n_- in s-*trans*-glyoxal (symmetry C_{2h}).

The theoretical predictions of *Swenson* and *Hoffmann*[2] are confirmed by the results of this photoelectron-spectroscopic investigation. In Table 1 are given the differences

$$\Delta(n) = I_v(\psi_J) - I_v(\psi_K)$$

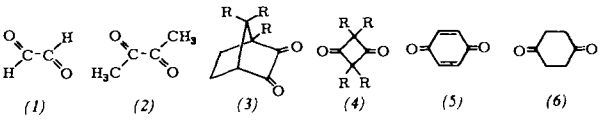
between the vertical ionization potentials $I_v(\psi_J)$ and $I_v(\psi_K)$ of those bands that are assigned in the photoelectron spectrum to an ionization process in which the photoelectron vacates those molecular orbitals to which n_+ and n_- contribute with maximum weight. If the validity of *Koopmans'* theorem[4] is assumed, *i.e.*, if

$$I_v(\psi_J) = -\varepsilon_J \text{ and } I_v(\psi_K) = -\varepsilon_K$$

then $\Delta(n)$ observed should correspond to the difference in the orbital energies of the molecular orbitals ψ_J and ψ_K:

$$\Delta(n) = \varepsilon_K - \varepsilon_J$$

Table 1. Experimental and theoretical splittings $\Delta(n)$ of dicarbonyl compounds. Column 1: no. of compound. Column 2: symmetry of the preferred conformation. Column 3: vertical ionization potentials, position of the maximum of those bands in the photoelectron spectrum to which the orbitals ψ_J and ψ_K are assigned. Column 4: experimental splitting $\Delta(n)$. Column 5: calculated splitting $\Delta(n)$, as obtained from the extended Hückel theory (EHT). All values are given in eV.



1	2	3		4	5
		$I_v(\psi_J)$	$I_v(\psi_K)$	$\Delta(n)$	$\Delta(n)$ EHT
(1)	C_{2h}*(trans)* [a]	10.59 [6]	12.19	1.6	1.49
(2)	C_{2h}*(trans)* [a, b]	9.55	11.43	1.9	1.67
(3)	C_1(R = CH_3)	8.80	10.40	1.6	–
	C_s(R = H)	–	–	–	1.50 [c]
(4)	D_{2h}(R = CH_3)	8.80	9.53	0.7	0.90
	D_{2h}(R = H)	–	–	–	0.75
(5)	D_{2h} [a]	10.03	10.93	0.9	0.77 [a, d]
(6)	D_2(twist?)	9.6_5	9.80	*ca.* 0.1_5	–

[a] Geometry according to data in [8].
[b] Symmetry under the assumption of axially symmetric methyl groups.
[c] In [2]: 0.68 eV, geometry unspecified.
[d] In [2]: 0.47 eV, geometry unspecified.

Remarks:

1. For two carbonyl groups bonded directly to one another, as in glyoxal *(1)*, biacetyl *(2)*, and camphorquinone *(3)*, the theory requires that $\Delta(n)$ is almost independent of the torsion angle φ. [EHT results for *(1)*: φ = 0° (s-*cis*), $\Delta(n) = 1.49$ eV; φ = 90°, $\Delta(n) = 1.62$ eV; φ = 180° (s-*trans*), $\Delta(n) = 1.48$ eV]. In particular—though perhaps surprisingly—the splitting $\Delta(n)$ for the s-*cis*- and s-*trans*-configurations should be the same. This conclusion is confirmed by the results found for *(1)*, *(2)*, and *(3)* (see Table 1).

2. In 2,2,4,4-tetramethyl-1,3-cyclobutanedione *(4)* the "through-bond" interaction between the two linear combinations n_+ and n_- and the C—C σ-orbitals of the cyclobutane ring[5] take place in such a way that the orbital assigned to the irreducible representation B_{2u} of D_{2h} is 0.7_5 eV higher in energy than the B_{3g} orbital (cf. Fig. 2).

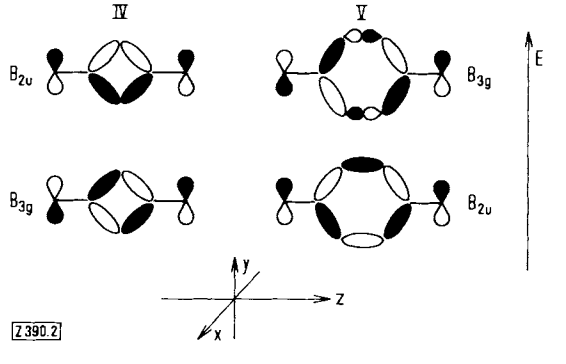


Fig. 2. Schematic diagram of the molecular orbitals ψ_J and ψ_K of 1,3-cyclobutanedione and *p*-benzoquinone to which the linear combinations n_+ and n_- make the largest contributions (symmetry D_{2h}).

3. For *p*-benzoquinone *(5)*, the splitting required by theory for those molecular orbitals to which n_+ and n_- contribute most, yields an assignment of the bands in the photoelectron

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spectrum of *(5)* which differs from that given previously[6]. This leads to the sequence $n, \pi, n, \pi, \ldots$ for the four uppermost occupied molecular orbitals (arranged in order of decreasing energy) and not to $n, n, \pi, \pi, \ldots$ as originally presumed. In this case, unlike that of *(4)*, the order of the orbitals referring to the irreducible representations B_{2u} and B_{3g} is reversed.

4. In the photoelectron spectrum of 1,4-cyclohexanedione *(6)* the splitting $\Delta(n)$ cannot be determined unambiguously. The band assigned to the ionization of the "lone" electron



(7)

pairs is somewhat broadened and its shape near the maximum is indicative of a splitting of $\Delta(n) = 0.1_5$ eV. Such a small value suggests that the twist conformation *(7)* (symmetry D_2)[7] is the preferred one.

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[1] Part 24 of Applications of Photoelectron Spectroscopy. This work is part of Project No. SR 2.120.69 of the Schweizerischer Nationalfond. —Part 23: *P. Bischof, E. Heilbronner, H. Prinzbach,* and *H. D. Martin,* Helv. Chim. Acta, in press.

[2] *J. R. Swenson* and *R. Hoffmann,* Helv. Chim. Acta *53*, 2331 (1970).

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[4] *T. Koopmans,* Physica *1*, 104 (1933); *W. G. Richards,* J. Mass Spectrom. Ion Physics *2*, 419 (1969).

[5] *L. Salem* and *J. S. Wright,* J. Chem. Soc. *D 1969*, 1370; J. Amer. Chem. Soc. *91*, 5947 (1969); *L. Salem,* Chem. Brit. *5*, 449 (1969); *P. Bischof, E. Haselbach,* and *E. Heilbronner,* Angew. Chem. internat. Edit. *9*, 953 (1970); *R. Hoffmann* and *R. B. Davidson,* private communication.

[6] *D. W. Turner, C. Baker, A. D. Baker,* and *C. R. Brundle:* Molecular Photoelectron Spectroscopy. Wiley-Interscience, London 1970.

[7] *P. Dowd, Th. Dyke,* and *W. Klemperer,* J. Amer. Chem. Soc. *92*, 6327 (1970).

[8] Tables of Interatomic Distances and Configuration in Molecules and Ions. Special Publication No. 11, The Chemical Society, London 1958.

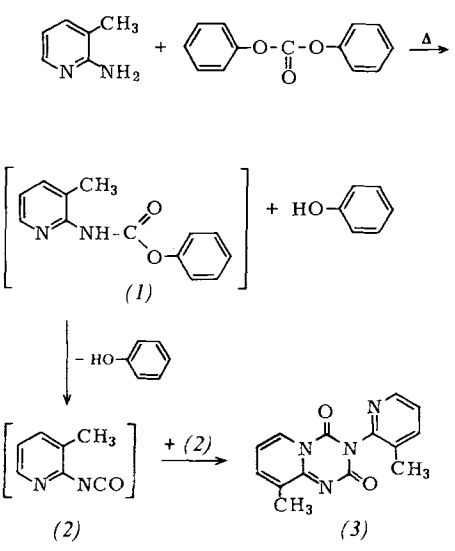
Pyridine, Pyrimidine, and Pyrazine Derivatives with an Isocyanato Substituent Vicinal to Nitrogen

By *Ulrich von Gizycki*[*]

No derivative of pyridine, pyrimidine, or pyrazine has previously been isolated in which an isocyanato group occurs in the vicinal position to nitrogen. 2-Isocyanatopyridine could be obtained only as dimer[1]; and 2-isocyanato-3-methylpyridine *(2)* is stable only in its dimeric form *(3)*, m.p. 212–215 °C. This dimer *(3)* is obtained in quantitative yield by reaction of 3-methyl-2-pyridinamine with diphenyl carbonate *via* the intermediates *(1)* and *(2)*.

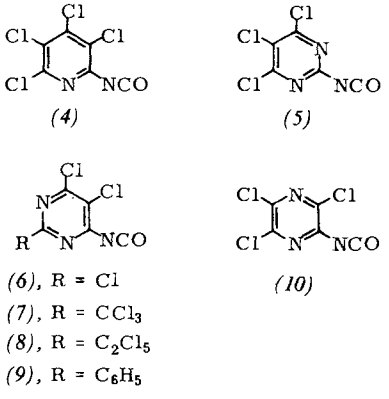
We have found that electronegative substituents hinder this dimerization, so that 2-pyridinamines substituted in this way can be converted into the monomeric isocyanato derivatives. This reaction occurs very smoothly when the aminoheterocycle is treated with oxalyl chloride. It can be applied also to pyrimidinamines and pyrazinamines.

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(1) *(2)* *(3)*

The isocyanato derivatives *(4)* to *(10)* have been prepared for the first time in this way.



(4) *(5)*

(6), R = Cl
(7), R = CCl_3
(8), R = C_2Cl_5
(9), R = C_6H_5

(10)

They are distillable colorless liquids or solids of high reactivity (Table 1). In their IR spectra the NCO band lies at 2250 cm^{-1}.

Table 1. Properties of the isocyanato derivatives *(4)* to *(10)*.

	B.p. (°C/torr)	At room temp.	Yield (%)
(4)	101–102/0.06	Solid	85
(5)	90–91/0.06	Solid	90
(6)	81–82/0.1	Liquid	90
(7)	115–117/0.1	Liquid	75
(8)	143–144/0.08	Solid	72
(9)	147–148/0.1	Solid	95
(10)	100/0.07	Solid	70

The corresponding urethanes (Table 2) are obtained smoothly by reaction with alcohols.

Table 2. Melting points of the urethanes prepared from the isocyanate derivatives *(4)* to *(10)*.

Isocyanate	Alcohol	M.p. (°C)
(4)	Ethanol	131–132
(5)	Cyclohexanol	144–145
(6)	1-Butanol	106–108
(7)	1,3-Dichloro-2-propanol	88–90
(8)	1,3-Dichloro-2-propanol	97–98
(9)	1,3-Dichloro-2-propanol	160–162
(10)	Allyl alcohol	80

Experimental:

The α-aminoheterocycle (0.1 mol) is dissolved in anhydrous benzene or toluene and dropped into a boiling mixture of oxalyl chloride (0.4–0.5 mol) and anhydrous benzene or toluene (1–2 mol). The whole is boiled under reflux until evolution of gas is completed (2–6 h). After filtration (crystalline precipitates that are sometimes formed consist of the bisoxamides) and removal of solvent by distillation, the residue is distilled in a vacuum.

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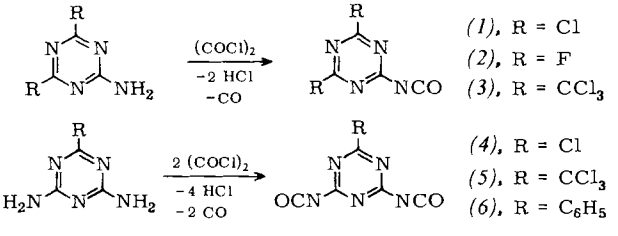
[1] *U. v. Gizycki* and *G. Oertel*, Angew. Chem. *80*, 363 (1968); Angew. Chem. internat. Edit. *7*, 381 (1968).

Isocyanato-*s*-triazines

By *Ulrich von Gizycki*[*]

Only one isocyanato-*s*-triazine, namely the 2,4-dichloro-6-isocyanato derivative *(1)*, has previously been isolated, and that from tetrameric cyanogen chloride by a route that cannot be generalized[1].

We have found that mono- and di-isocyanato derivatives of *s*-triazine can be readily prepared in good yield by reaction of the appropriate *s*-triazinamine with oxalyl chloride.



(1), R = Cl
(2), R = F
(3), R = CCl_3
(4), R = Cl
(5), R = CCl_3
(6), R = C_6H_5

The isocyanato derivatives *(1)*–*(6)* are colorless solids or liquids that distil without decomposition and are highly reactive (Table 1). In their IR spectrum the NCO band lies at 2250 cm^{-1}. The reaction proceeds better the more electronegative is the substituent R.

Table 1. Properties of the isocyanates *(1)* to *(6)*.

Isocyanate	B. p. (°C/torr)	At room temp.	Yield (%)
(1)	105–106/10–12	Solid	93
(2)	147.5/760	Liquid	70
(3)	134–135/0.2–0.3	Solid	70
(4)	84–85/0.2	Solid	85
(5)	126–127/0.9	Liquid	84
(6)	152–153/0.3	Solid	75

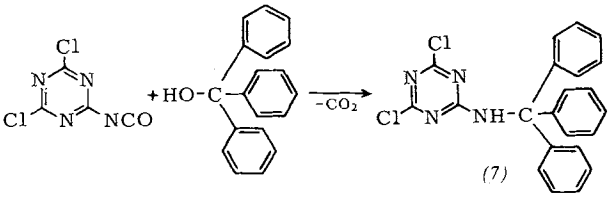
Table 2. Melting points of the urethanes prepared from the isocyanates *(1)* to *(6)*.

Isocyanate	Alcohol	M. p. (°C)
(1)	1,3-Dichloro-2-propanol	124–125
(2)	Phenol	136–137
(3)	1-Butanol	105–108
(4)	Phenol	161–163
(5)	1,3-Dichloro-2-propanol	110–114 [a]
(6)	Phenol	Dec. from 215

[a] Contains solvent (CCl_4).

The isocyanates *(1)* to *(6)* react smoothly with alcohols or phenols, yielding urethanes or diurethanes (Table 2).

Reaction with triphenylmethanol at 0–20 °C affords the urethanes which at higher temperatures lose CO_2 with formation of the tritylated *s*-triazinamines, *e.g.*, *(7)*, m. p. 191–193 °C.



(7)

Experimental:

Finely powdered *s*-triazinamine (0.1 mol) is suspended in a mixture of oxalyl chloride (0.3–0.5 mol per amino group) and anhydrous toluene or chlorobenzene (1–2 mol) [but distilled thiophane dioxide for *(2)*], and the mixture is boiled under reflux until evolution of gas is complete (7–8 h). After filtration and removal of solvent by distillation, the residue is distilled in a vacuum.

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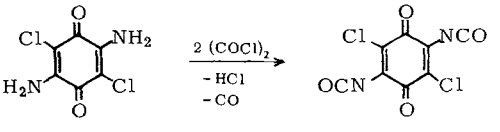
[1] *Y. Kodoma* and *T. Sekiba*, J. Soc. Org. Syn. Chem., Japan *21*, 888 (1963).

Isocyanatoquinones

By *Ulrich von Gizycki*[*]

Quinones carrying an isocyanato substituent in the quinonoid ring have so far been unknown. We now report syntheses of two representatives of this new class of compound.

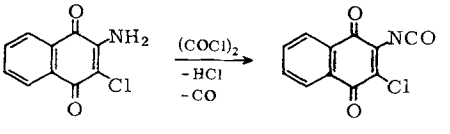
When a mixture of finely powdered 2,5-diamino-3,6-dichloro-1,4-benzoquinone (100 g), oxalyl chloride (400 g), anhydrous butyl acetate (200 ml), and anhydrous chlorobenzene (550 ml) is boiled under reflux until gas evolution ceases (~36 h), then, on cooling, red needles of 2,5-dichloro-3,6-diisocyanato-1,4-benzoquinone *(1)* (about 50 g) separate.



(1)

M. p. of *(1)*: 259—260 °C. IR: NCO band at 2205 cm^{-1}, CO at 1665 and 1675 cm^{-1}. Bis(ethylurethane): orange needles, m. p. 220—221 °C.

Yellow 2-chloro-3-isocyanato-1,4-naphthoquinone *(2)* was obtained analogously in 75% yield from 2-amino-3-chloro-1,4-naphthoquinone (50 g) and oxalyl chloride (200 g) in anhydrous *o*-dichlorobenzene.



(2)

The isocyanate *(2)* crystallizes after filtration and concentration of the solution to one-third of its volume.

M. p. of *(2)*: 140—142 °C. IR: NCO band at 2200 cm^{-1}, CO at 1670 cm^{-1}. Ethylurethane: yellow needles, m. p. 135—136 °C.

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Bond-Bond Interaction in Polysilanes[1]

By *Hans Bock* and *Walther Ensslin*[*]

Linear methylpolysilanes $H_3C-[Si(CH_3)_2]_k-CH_3$ are the more readily excited the longer the chain length k: the long-wavelength UV bands approach the edge of the visible spectral region[2,3] and the mass-spectroscopically determined first ionization energies IE_1[2,3] are always lower than those of the corresponding polyenes. The various IE_1 values have previously been interpreted[2] by means of the "Sandorfy C" model which was developed for alkanes and which approaches σ-molecular orbitals by linear combinations of sp^3 hybrid orbitals (Fig. 1).

The basic method of calculation uses the empirically calibrated ratio $m=\beta_{geminal}:\beta_{vicinal}$[4] and predicts an asymmetrical splitting of the eigenvalues ε_n (Fig. 1: ε_1 and ε_2) relative to α_{SiSi}. To verify the splitting scheme it was of interest to measure the higher ionization energies IE_n ($n>1$) of polysilanes.

Photoelectron (PE) spectrometry provides the energy differences IE_n between the ground state of a neutral molecule and the states of its radical cation, which, if the validity of *Koopmans*' theorem[5] is assumed, can be correlated with the negative SCF eigenvalues ε_n of the ground-state molecular orbitals. Fig. 2 shows the PE spectra[6] of the linear ($k=1$, 2, 3, 4) methylsilanes, the branched tetrakis(trimethylsilyl)silane, and the cyclic derivatives $[Si(CH_3)_2]_r$ ($r=5$ or 6). The corresponding numerical values are given in Table 1.

Fig. 1. Linear combination and eigenvalue scheme according to the "Sandorfy C" model.

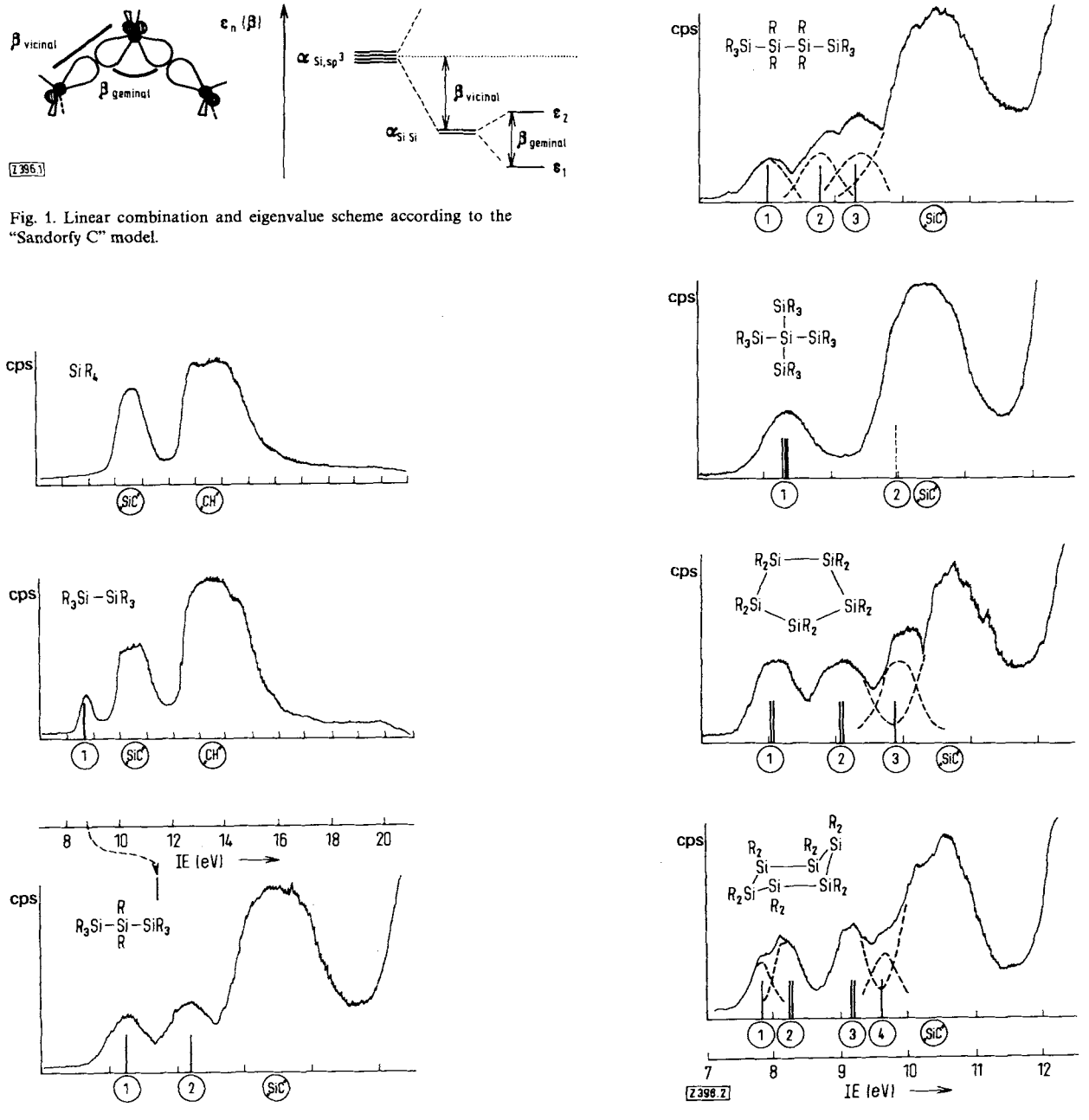


Fig. 2. PE spectra of linear, branched, and cyclic methylsilanes (R = CH_3).

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Table 1. Vertical ionization energies IE_n (eV) of the PE bands n.

Compound		①	②	③	④	(SiC)
$R-(SiR_2)_k-R$	$k=1$					10.5
	$k=2$	8.69				10.4
	$k=3$	8.19	9.14			10.4
	$k=4$	7.98	8.76	9.30		10.5
$Si(SiR_3)_4$		8.24	(9.9)			10.4
$(SiR_2)_r$	$r=5$	7.94	8.91	9.80		10.7
	$r=6$	7.79	8.16	9.12	9.78	10.4

Comparison of the PE spectra of tetramethylsilane and hexamethyldisilane shows that in the latter the largely unchanged, intense "SiC" and "CH" band systems are preceded by an isolated band that has to be ascribed to the ionization from a molecular orbital with a preponderant SiSi contribution. This assignment is confirmed by the appearance of two and three bands, respectively, of comparable intensity in the PE spectra of silane chains with $k=3$ and $k=4$. Retention of the midpoint in this "splitting" shows that "SiC" and "CH" contributions to the "SiSi" molecular orbitals are negligible. From the tetrahedral symmetry of the Si_5 skeleton of tetrasilylsilane, one would expect a 3:1 splitting into t_2 and a_1 molecular orbitals; in the PE spectrum the t_2 band is at 8.24 eV, and the a_1 band is indicated to lie within the "SiC" peak at about 9.9 eV. Cyclic silanes should show intensity patterns 2:2:1 (D_{5h}: $e_1'+e_2'+a_1'$) and 1:2:2:1 (chair form D_{3d}: $a_{1u}+e_g+e_u+a_{1g}$), in which the last band always falls under the initial ascent of the following "SiC" band system and thus shows an exaggerated intensity.

These findings can be rationalized by a simple LCBO (linear combination of bond orbitals) model (Fig. 3).

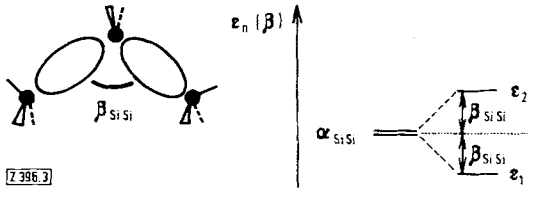


Fig. 3. Bond-bond interaction and eigenvalue scheme according to the LCBO model.

The internal parametrization is carried out using the ionization energy of hexamethyldisilane ($IE_1=8.69$ eV $=\alpha_{SiSi}$), which also absorbs end-group effects and other neglected interactions. The coefficients x_n of the orbital eigenvalues $\varepsilon_n=\alpha_{SiSi}+x_n\beta_{SiSi}$ can be taken from HMO tables[7]. The resulting linear regression (Fig. 4):

$$IE_n = 8.69\text{ eV} + x_n\,0.5\text{ eV}$$

has the small standard deviation SE = 0.02 eV.

From the excellent correlation between the experimental and the calculated values (Fig. 4) several conclusions can be drawn. First the delocalization of electrons in σ-skeletons becomes particularly obvious in the case of the methylpolysilanes, because the PE ionization energies can be interpreted in terms of a simple model. Further, the applicability of *Koopmans'* theorem indicates comparable stabilization of the radical cation states of straight-chain, branched, and cyclic methylpolysilanes. Moreover, since the LCBO approximation used is the border-line case of the "Sandorfy C" model in which the ratio $\beta_{geminal}:\beta_{vicinal}$ approaches zero, *i.e.*, $\beta_{vicinal}$ becomes very large, the influence of antibonding molecular orbitals of suitable symmetry must be negligibly small. Finally, a bonding contribution from unoccupied silicon orbitals of π-symmetry can also be excluded because the midpoint α_{SiSi} is retained in the splitting scheme.

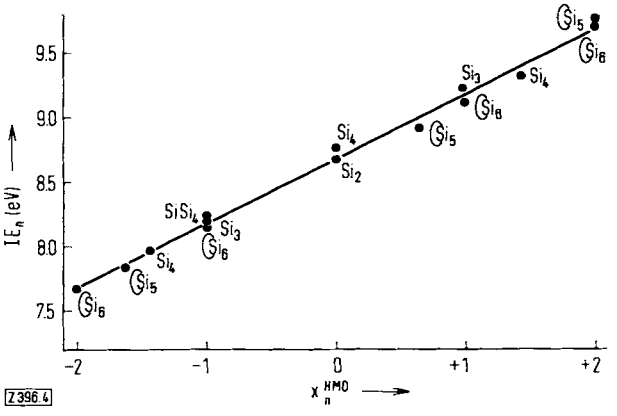


Fig. 4. Correlation of the vertical ionization energies IE (eV) of linear, branched, and cyclic polysilanes with HMO eigenvalue coefficients x_n.

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[1] Part 3 of Photoelectron spectroscopy and Molecular Properties.—Part 2: *H. Bock* and *W. Fuss*, Angew. Chem. *83*, 169 (1971); Angew. Chem. internat. Edit. *10*, 182 (1971).

[2] *C. G. Pitt, M. M. Bursey*, and *P. F. Rogerson*, J. Amer. Chem. Soc. *92*, 519 (1970), and references cited therein.

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[4] The ratio $m=\beta_{geminal}:\beta_{vicinal}$ for alkanes amounts to $m=0.34_{65}$ [*K. Fukui, H. Kato*, and *T. Yonezawa*, Bull. Chem. Soc. Japan *33*, 1197 (1960)] and for silanes $m=0.34_{58}$ [2]. The asymmetry caused by this is, however, only small since the quantity used in the calculation is $m^2/2=0.06$.

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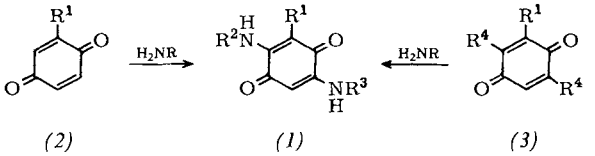
[6] The PE spectra were determined with a Perkin-Elmer PS 16 instrument ("He—I" lamp, electrostatic sector field 127°). All the numerical values given refer to the vertical ionization energies.

[7] Cf., *e.g., E. Heilbronner* and *H. Bock*: Das HMO-Model und seine Anwendung, Vol III: Tabellen berechneter und experimenteller Größen. Verlag Chemie, Weinheim 1970.

Oxidative Amination of Hydroquinones[1]

By *Wolfram Schäfer* and *Antonio Aguado*[*]

Substituted 2,5-diamino-1,4-benzoquinones *(1)* can be prepared by (a) 1,4-addition of primary amines to benzoquinones *(2)*, $R^1=H$, followed by oxidation[2] or (b) nucleophilic replacement of readily eliminable groups in *(3)*, $R^1=CH_3CO$ or $COOCH_3$, $R^4=Hal$, OCH_3, or SC_2H_5[3,4].



(2) *(1)* *(3)*

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In (a) maximally 50% of the quinone is converted into *(1)*, and in (b) the preparation of the starting material is demanding[5]. Oxygen in the presence of copper sulfate has been recommended[6, 7] for oxidation of the substituted hydroquinones formed as intermediates by the 1,4-addition, but this method is successful only with secondary alkylamines. 4,5-Dianilino-1,2-benzoquinone is formed from pyrocatechol in the presence of aniline and silver oxide in glacial acetic acid[8].

We have found that substituted 2,5-bis(arylamino)-1,4-benzoquinones *(1)* can be prepared in good yield and purity by oxidizing the hydroquinones corresponding to *(2)* with sodium iodate in the presence of the amine (Table 1).

Table 1. 2,5-Bis(arylamino)-1,4-benzoquinones *(1)* prepared by oxidative amination.

R^1	$R^2=R^3$	Dec. pt. (°C)	Yield (%)
$COCH_3$	C_6H_5	199	91
	C_6H_4-*o*-CH_3	183	85
	C_6H_4-*m*-Cl	179	83
	C_6H_4-*p*-OCH_3	216	86
	3-pyridyl	222	81
$COOCH_3$	C_6H_5	202	89
	C_6H_4-*o*-CH_3	217	87
	C_6H_4-*m*-Cl	212	89
	C_6H_4-*o*-Cl	193	88
	C_6H_4-*p*-OCH_3	226	89
CH_3	C_6H_5	147	72
Br	C_6H_5	307	63
$CON(CH_3)_2$	C_6H_5	245	80

General procedure:

A solution of hydroquinone (0.1 mol) and arylamine (0.22 mol) in methanol/water (2—3 l; amount and proportions depending on the solubility of the components) is stirred vigorously with sodium iodate (0.3 mol) for 5—20 h. The product that is precipitated is filtered off, washed, and crystallized from alcohol.

The arylamino group on C-2 of *(1)*, $R^1=COCH_3$ or $COOCH_3$, $R^2=R^3=$aryl, can be replaced by primary amino groups; with alkylamines the reaction occurs quantitatively within a few minutes (faster with acetyl- than with ester-quinones), and with arylamines the replacement can be forced by an excess of reagent and higher reaction temperature (boiling methanol or butanol). The structures of the products are proved (Table 2) by considering the amino group that is replaced[9]. The exchange of amino groups makes unsymmetrically substituted 2,5-diamino-1,4-benzoquinones readily accessible for the first time.

Table 2. Substituted 2-(alkylamino)-5-(arylamino)- and 2,5-bis(arylamino)-1,4-benzoquinones *(1)* synthesized by amine exchange.

R^1	R^2	R^3	Dec. pt. (°C)
$COCH_3$	H	C_6H_5	282
	CH_3	C_6H_5	138
	C_2H_5	C_6H_5	128
	H	C_6H_4-*p*-CH_3	270
	CH_3	C_6H_4-*p*-CH_3	146
	CH_3	C_6H_4-*p*-Cl	219
	C_2H_5	C_6H_4-*p*-Cl	162
	C_6H_5	C_6H_4-*m*-Cl	186
	C_6H_4-*p*-CH_3	C_6H_5	207
$COOCH_3$	H	C_6H_5	263
	CH_3	C_6H_5	221
	C_2H_5	C_6H_5	161
	n-C_4H_9	C_6H_4-*p*-CH_3	147
	H	C_6H_4-*m*-Cl	254
	CH_3	C_6H_4-*m*-Cl	223
	C_2H_5	C_6H_4-*m*-Cl	188
	n-C_4H_9	C_6H_4-*p*-F	156
	n-C_4H_9	C_6H_4-*p*-CN	194
	CH_3	C_6H_4-*p*-OCH_3	245
	CH_3	C_6H_4-*p*-F	249
	C_6H_4-*p*-Cl	C_6H_5	209

General procedure:

The alkylamine (0.2 mol) is added to a solution of *(1)*, $R^1=COCH_3$ or $COOCH_3$, $R^2=R^3=$aryl (0.1 mol), in methanol or methanol-tetrahydrofuran and the reaction is followed by thin-layer chromatography. The solution is concentrated as soon as the starting material has disappeared, and the crude product is recrystallized from methanol or glacial acetic acid.

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[1] Part 8 of The Chemistry of Substituted Benzoquinones. — Part 7: *W. Schäfer*, Chem. Ber. in press. The content of this paper was read at Hamburg on March 16, 1971.

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[7] *A. H. Crosby* and *R. H. Leitz*, J. Amer. Chem. Soc. *78*, 1233 (1956).

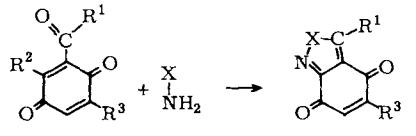
[8] *F. Kehrmann* and *M. Cordone*, Ber. dtsch. chem. Ges. *46*, 3009 (1913); *V. B. Barry, J. G. Belton, J. F. O. Sullivan*, and *D. Towney*, J. Chem. Soc. *1958*, 859.

[9] *W. Schäfer, A. Aguado*, and *U. Sezer*, Angew. Chem. *83*, 442 (1971); Angew. Chem. internat. Edit. *10*, 406 (1971).

A New Method of Preparing Heterocyclic Quinones[1]

By *Wolfram Schäfer, Antonio Aguado*, and *Utku Sezer*[*]

The substituted quinones *(1a)* to *(1e)*[2–4] can be used as starting materials for synthesis of heterocyclic quinones by condensations leading to a heterocyclic ring.



(1) *(2)*

	R^1	R^2	R^3
(1a)	CH_3	OCH_3	OCH_3
(1b)	OCH_3	OCH_3	OCH_3
(1c)	OCH_3	Cl	OCH_3
(1d)	CH_3	[NHAlkyl,	NHAryl]
(1e)	CH_3	NHAryl	NHAryl
(1f)	CH_3	NH_2	[NHAlkyl, NHAryl]

Compound *(1a)* reacts smoothly with hydrazines or hydrazides in methanol at room temperature to give indazolequinones *(2a)* substituted on N-2 (see Table 1)

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by way of intermediate 2-hydrazinobenzoquinones. Quinones of type *(1d)* and *(1e)* react analogously with hydrazine itself, hydrazines, hydrazides, semicarbazide, or thiosemicarbazide in boiling methanol, to yield indazolequinones *(2b)* with a substituted amino group on C-5. These products can also be obtained by replacing the methoxy group in compound *(2a)*. Yields are between 73% and 95%. The acyl group of 2-acylindazolequinones, as of acylimidazoles[5], can be readily removed by hydrolysis. During reaction of *(1d)* and *(1e)* with acetylhydrazine, semicarbazide, or thiosemicarbazide, the acyl groups of the hydrazino compounds are removed.

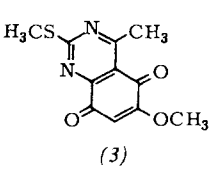
Benzoisoxazolequinone *(2c)* is formed in 80% yield from *(1c)* and sodium azide in methanol. 3-Acetyl-2,5-bis(arylamino)-1,4-benzoquinones[1] react with hydroxylamine in boiling methanol to give *ca.* 90% yields of the benzisoxazolequinones *(2d)*. Reductive opening of the isoxazole ring by phenylhydrazine or by catalytic hydrogenation and

Table 1. Indazolequinones and benzisoxazolequinones prepared.

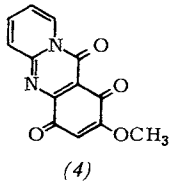
	R^1	R^3	X	Decomp. (°C)
(2a)	CH_3	OCH_3	N—CH_3	183
	CH_3	OCH_3	N—C_6H_5	217
	CH_3	OCH_3	N—C_6H_4-*p*-NO_2	*ca.* 260
	CH_3	OCH_3	N—$COCH_3$	193
	CH_3	OCH_3	N—COC_6H_5	222
	CH_3	OCH_3	N—SO_2—C_6H_4-*p*-CH_3	178
	CH_3	OCH_3	N—SO_2—C_6H_4-*p*-NO_2	210
(2b)	CH_3	NHC_6H_5	N—CH_3	228–230
	CH_3	$N(CH_3)_2$	N—C_6H_5	220
	CH_3	$NHCH_3$	N—C_6H_5	251
	CH_3	NHC_6H_5	N—C_6H_5	191
	CH_3	$N(CH_3)_2$	N—C_6H_4-*p*-NO_2	248–260
	CH_3	NHC_6H_5	N—C_6H_4-*p*-NO_2	277–281
(2c)	OCH_3	OCH_3	O	241
(2d)	CH_3	NHC_6H_5	O	197
	CH_3	NHC_6H_4-*p*-CH_3	O	180
	CH_3	NHC_6H_4-*m*-Cl	O	199
	CH_3	NHC_6H_4-*o*-Cl	O	185

subsequent oxidation of the intermediate hydroquinone by air leads to the 2-amino-1,4-benzoquinones *(1f)* and *(1g)*, which are also obtained from *(1d)* and *(1e)* by means of ammonia. The reaction provides proof of the structure of the quinones *(2)*.

Reaction of *(1a)* or *(1b)* with compounds containing the structural elements of an amidine leads to quinones to which a six-membered heterocycle is fused: *S*-methylthiuronium sulfate and *(1a)* in the presence of sodium methoxide in methanol yield 6-methoxy-4-methyl-2-(me-



(3)



(4)

thylthio)quinazoline-5,8-quinone *(3)* in 65% yield (m.p. 188 °C), and *(1b)* reacts with 2-aminopyridine to give 7-methoxy-5-oxo-5*H*-pyrido[2,1-*b*]quinazoline-6,9-quinone *(4)* in 79% yield (dec. *ca.* 290 °C).

The structures of the products were proved by elemental analyses and spectroscopic measurements (MS, IR, UV, and NMR) as well as by the synthetic routes.

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[1] Part 9 of The Chemistry of Substituted Benzoquinones. — Part 8: *W. Schäfer* and *A. Aguado*, Angew. Chem. *83*, 441 (1971); Angew. Chem. internat. Edit. *10*, 405 (1971). The content of this paper was read at Hamburg on March 16, 1971.

[2] *W. Schäfer* and *R. Leute*, Chem. Ber. *99*, 1632 (1966).

[3] *W. Schäfer*, *R. Leute*, and *H. Schlude*, Tetrahedron Lett. *1967*, 4303.

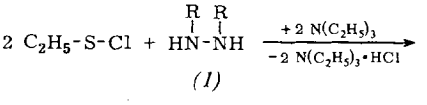
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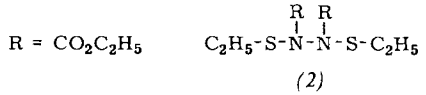
Preparation of Some Hydrazine Derivatives Containing Nitrogen-Sulfur Bonds[**][1]

By *Karl-Heinz Linke*, *Rudolph Bimczok*, and *Herbert Lingmann*[*]

Diels and *Wulff*[2] were able to add ethanethiol to the N=N double bond of diethyl azodicarboxylate to obtain diethyl 1-(ethanesulfenyl)hydrazine-1,2-dicarboxylate. An attempt by us to synthesize this compound by reaction of ethanesulfenyl chloride with diethyl hydrazine-1,2-dicarboxylate *(1)* in the presence of triethylamine afforded instead diethyl 1,2-bis(ethanesulfenyl)hydrazine-1,2-dicarboxylate *(2)*, a distillable oil (b.p. 54—56 °C/0.01 torr), which was identified by analysis and its IR spectrum.

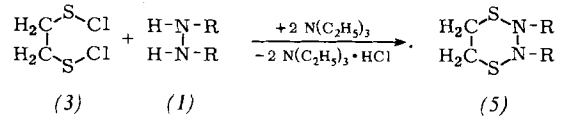


(1)

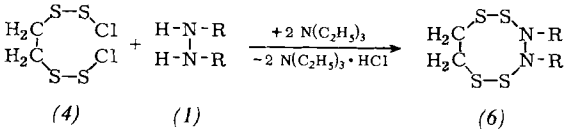


(2)

The molecule peak ($m/e = 296$) did not appear in the mass spectrum of *(2)*, which however showed a fragment of half this mass with great intensity, which is to be explained by cleavage of the N—N bond. As formation of disubstituted products is clearly favored and as the stability of ring compounds is expected to be greater[3], we treated 1,2-bis(chlorosulfenyl)ethane *(3)*[4] and 1,2-bis(chlorodisulfanyl)-



(3) *(1)* *(5)*



(4) *(1)* *(6)*

R = $CO_2C_2H_5$

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ethane *(4)*[5] with *(1)* in the presence of triethylamine and we thus obtained the cyclic compounds diethyl 1,4,2,3-dithiadiazacyclohexane-2,3-dicarboxylate *(5)* and 1,2,5,6,3,4-tetrathiadiazacyclooctane-3,4-dicarboxylate *(6)*, respectively.

Formation of the six-membered ring is favored to such an extent that it is unnecessary to use the dilution technique for the preparation. The two compounds are colorless crystalline substances: *(5)* m.p. 90°C (dec); *(6)* m.p. 94–95°C. They were characterized by elemental analysis, IR and mass spectra, and chemical degradation.

There is no N—H vibration in the IR spectra. The N—N stretching vibrations and the S—S stretching vibration in compound *(6)* can, however, be discerned. Both compounds break down in the mass spectrometer in similar ways: after removal of the ester groups the two nitrogen atoms are lost simultaneously as N_2, whence the existence of N—N bonds can be concluded. That these heterocycles are hydrazine derivatives was confirmed also by degradative reactions: *(1)* is formed on desulfuration of *(5)* or *(6)* with Raney nickel.

Experimental:

Compound *(5)*: The chloride *(3)* (4.1 g, 0.025 mol), dissolved in ether (50 ml), is add dropwise during 30 min into a vigorously stirred solution of *(1)* (17.6 g, 0.1 mol) and triethylamine (5.1 g, 0.05 mol) in anhydrous ether (500 ml) at 0°C. After 3 hours' stirring, filtration from triethylammonium chloride and cooling, the product *(5)* crystallizes. It is recrystallized from ether. Yield: 4.5 g (67%).

Compound *(6)*: *(1)* (4.4 g, 0.025 mol) and triethylamine (5.1 g, 0.05 mol) are dissolved in dioxane (150 ml). *(4)* (5.7 g, 0.025 mol) is diluted with ether (150 ml). The two solutions are dropped simultaneously during 3 h into vigorously stirred anhydrous ether (250 ml) at 0°C. When reaction is complete, the mixture is filtered and the solvent is removed. The product *(6)* is isolated by preparative thin-layer chromatography with dichloromethane on silica gel H (R_F=0.4). Yield: 1.0 g (12%).

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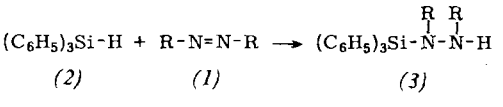
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Hydrosilylation of a N=N Double Bond[**][1]

By *Karl-Heinz Linke* and *Hans Jürgen Göhausen*[*]

Although hydrosilylation of olefins and acetylenes is of great preparative importance[2], no corresponding reaction with an azo compound as unsaturated component has previously been reported. During our investigations of addition reactions of diethyl azodicarboxylate *(1)*[3] we have added triphenylsilane *(2)* by its Si—H group to the N=N double bond of the azo ester with formation of diethyl (triphenylsilyl)-1,2-hydrazinedicarboxylate *(3)*.



$(C_6H_5)_3Si\text{-}H + R\text{-}N{=}N\text{-}R \rightarrow (C_6H_5)_3Si\text{-}\overset{R}{\underset{|}{N}}\text{-}\overset{R}{\underset{|}{N}}\text{-}H$

(2) *(1)* *(3)*

R = $CO_2C_2H_5$

The reaction is effected either in boiling benzene or at room temperature in the same solvent under irradiation by UV light[4]. Addition of di-*tert*-butyl peroxide greatly increased the yield (Table 1), so the addition clearly occurs by a radical mechanism.

Table 1. Yields of *(3)* under various conditions. The initial solution was in all cases 0.32 M in *(1)* and *(2)*.

Reaction conditions	Reaction time	Yield (%)
Boiling benzene without peroxide	11 days	15.3
Boiling benzene with peroxide	11 days	71.5
Irradiation without peroxide	3.5 h	20.6
Irradiation with peroxide	3.5 h	77.0

Compound *(3)* is soluble in all the usual organic solvents except light petroleum and crystallizes in colorless needles, m.p. 117–118°C (dec). It was characterized by elemental analysis, IR spectrum, and mass spectrum.

The IR spectrum showed the N—H stretching vibration at 3295 cm^{-1}, two C=O bands at 1745 and 1700 cm^{-1}, and C—H stretching vibrations at 3075, 3005, and 2980 cm^{-1}. Further strong absorptions occur at the following wave numbers: 1515, 1430, 1372, 1310, 1240, 1112, 1050, 740, 705, 695, 530, and 505 cm^{-1}.

The 70-eV mass spectrum of *(3)* shows, besides the molecular ion at m/e=434, only one fragment in which the Si—N—N skeleton remains intact, namely, $M^+ - (C_6H_5 + H)$, m/e=356. This is accompanied by fragments $(C_6H_5)_3Si^+$ (m/e=259) and

$$N(CO_2C_2H_5)\text{—}NH\text{—}CO_2C_2H_5^+ \quad (m/e=175)$$

whose further degradation can also be followed.

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π-Allylpentakis(trifluorophosphine)tantalum[1]

By *Thomas Kruck* and *Hans-Ulrich Hempel*[*]

Transition metals for which trifluorophosphine complexes have so far been reported belong to Groups 6A, 7A, and 8[2]. We have now prepared a PF_3 complex of a metal of

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Group 5 A by treatment of an ethereal solution of tetrakis-(π-allyl)tantalum *(1)*[3] with an excess of trifluorophosphine under pressure, whereupon π-allylpentakis(trifluorophosphine)tantalum *(2)* was formed.

$$2\ (\pi\text{-}C_3H_5)_4Ta + 10\ PF_3 \xrightarrow[20\,^\circ C]{20\ atm.}$$

(1)

$$2\ (\pi\text{-}C_3H_5)Ta(PF_3)_5 + 3\ C_6H_{10}$$

(2)

Compound *(2)* sublimes at room temperature and 10^{-4} torr and forms ruby-red crystals that can be kept without decomposition under nitrogen at −35 °C. In the solid state, *(2)* is stable in air at room temperature for some time, but decomposes even under nitrogen within a few days at 20 °C.

The mass spectrum of *(2)* at 20 eV shows the molecular ion at $m/e = 662$ and fragments that arise by successive loss of PF_3 groups[4].

The assumption, based originally on the noble-gas rule, that the π-allyl group would be symmetrically bound was confirmed by the ^{1}H-NMR spectrum, which contained three signals with intensity ratios 1:2:2 at $\tau = 5.47$ *(meso)*, 7.50 *(syn)* and 8.68 *(anti)*[5].

The form of the P—F vibrations in the IR spectrum resembles that of halogenopentakis(trifluorophosphine)rhenium complexes[6], thus suggesting that the PF_3 groups form a distorted square pyramid, with the allyl group lying over the basal plane of the pyramid.

Attempts to replace all four allyl groups by trifluorophosphine to form the species $[Ta(PF_3)_6]$ have so far all failed, and reactions of *(1)* with PF_3/H_2 mixtures under increased pressure, which could have led to $HTa(PF_3)_6$, afforded only metallic tantalum and propane.

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German version: Angew. Chem. *83*, 437 (1971)

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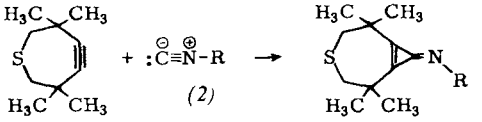
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[1+2]Cycloadditions of Isocyanides to Alkynes[1] [**]

By *A. Krebs* and *H. Kimling*[*]

We report the formation of cyclopropenimines in [1+2]-cycloadditions of isocyanides to alkynes. Cyclopropenimines have been postulated as intermediates in reactions of isocyanides with electron-deficient alkynes but so far have not been isolated from such systems[2-4]. We have now obtained cyclopropenimines from strained cyclic or electron-rich alkynes and isocyanides; in these cases the cyclopropene system is not destabilized by electron-withdrawing substituents at the C=C-double bond. Thus, 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne *(1)*[5] reacts in benzene with the isocyanides *(2a)–(2c)* to give *(3a)–(3c)*; the rate of addition decreases considerably in the order *(2a)* > *(2b)* > *(2c)* (Table 1).



(1) *(2)* *(3)*

(a), R = *p*-$O_2NC_6H_4$
(b), R = C_6H_5
(c), R = Cyclohexyl

Table 1. Time (*t*) for the addition of *(1)* to *(2a)–(2c)* at 25 °C. Yields and properties of *(3a)–(3c)*.

	t (days)[a]	Yield (%)	M.p. (°C)	IR (KBr, cm^{-1})
(3a)	0.12	80	156–158	1835
(3b)	3	78	122–124	1825
(3c)	14	36	146–148	1840

[a] *t*: Time for 90% conversion of *(1)* (determined by NMR, molar ratio 1:1, 0.5 M solution).
[b] From *(1)* and *(2c)* at least one other product is formed in addition to *(3c)*.

The structures of *(3a)—(3c)* were proved by elemental analysis, mass, ^{1}H-NMR and IR spectra[6, 7] as well as by hydrolysis to the ketone (m.p. 182 °C), which was also synthesized by addition of dichlorocarbene to *(1)* and subsequent hydrolysis.

The ^{1}H-NMR spectra of *(3a)—(3c)* are temperature dependent; at low temperatures the methyl groups appear as two singlets which coalesce at higher temperatures. The free enthalpies of activation $\Delta G_c^{\neq}$ for the *syn-anti* isomerizations were calculated (Table 2) from the coalescence temperatures T_c, the chemical shift differences Δν and the line widths b_E at low temperatures.

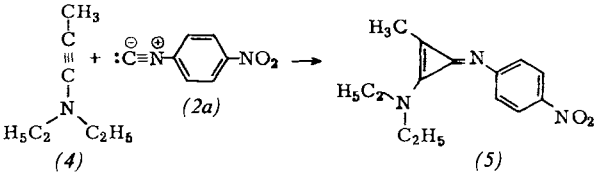
Table 2. ^{1}H-NMR data (60 MHz) and free enthalpies of activation $\Delta G_c^{\neq}$ for the *syn-anti* isomerization in *(3a)–(3c)*.

	Δν (Hz)	T_c (±2, °C)	b_E (Hz)	$\Delta G_c^{\neq}$ (±0.2, kcal/mole)
(3a)[a]	11.6	+ 8	2.5	14.7
(3b)[a]	8.8	+ 79	1.6	18.7
(3c)[b]	2.2	+145	1.6	23.8

[a] In $[D_8]$-toluene.
[b] In diphenyl ether.

Thus, the $\Delta G_c^{\neq}$ values and the influence of the *N*-substituents on the barrier to inversion are in the same order of magnitude as in other imines[8].

Diphenylacetylene, 2-butyne, and cyclooctyne do not react with the isocyanides *(2a)—(2c)* under analogous conditions to yield cyclopropenimines. However, 1-diethyl-



(4) *(2a)* *(5)*

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amino-1-propyne *(4)* adds *(2a)* with formation of *(5)* ($t = 12$ days at 25 °C).

The structure of *(5)* (m.p. 90—91 °C; yield 34%) was proved by elemental analysis, mass, ^{1}H-NMR and IR spectra (1880 cm^{-1}).

These additions may, like the analogous carbene reactions, proceed by a concerted (cheletropic) or a two-step mechanism[9]; investigations are in progress.

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New, Nonplanar *trans*-Stilbenes Exhibiting Nematic Phases at Room Temperature

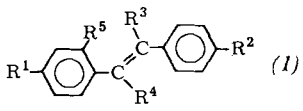
By *William R. Young, Arieh Aviram*, and *Robert J. Cox*[*]

In 1969, *Kelker* and *Scheurle* reported the preparation of *N*-(*p*-methoxybenzylidene)-*p*-*n*-butylaniline, which exhibits a nematic mesophase between 20 and 41 °C[1]. This compound suffers, however, from two drawbacks: it is yellow and it hydrolyzes in the presence of ambient moisture[2].

We have now investigated some *trans*-stilbene derivatives that are unique among the nematogenic azo[3], azoxy[3], azomethine[3], nitrone[4], and stilbene[3,5] compounds in combining an inherently colorless appearance with a relatively high degree of resistance toward moisture, long wavelength ultraviolet light, and oxygen.

In an earlier publication[5] we postulated that the high melting points of *trans*-stilbene and related *para*-substituted derivatives is a consequence of the planar configuration of these molecules[6], and it was hypothesized that nonplanar, low melting nematic materials could be prepared by the introduction of small, globular substituents in the *alpha*, *beta*, or *ortho* positions of the molecule. The use of alkyl substituents in the *para* positions might also prove beneficial, as has been demonstrated for the azomethines[1].

We have synthesized a series of *trans*-stilbene derivatives *(1)*. The precursors for all of these compounds are the appropriately substituted benzyl phenyl ketones, which were prepared by the standard Friedel-Crafts acylation procedure employing a phenylacetyl chloride and a benzene derivative. The stilbenes *(1a)* and *(1b)* were synthesized from the ketones by $LiAlH_4$ reduction, dehydration with $NaHSO_4$, and low temperature recrystallization. The methyl derivatives *(1c)* and *(1d)* were prepared from their appropriate ketones in an analogous manner, except that methylmagnesium iodide was employed as the reducing agent. The chloro compounds *(1e)* to *(1l)* were synthesized by reaction of benzyl phenyl ketones with phosphorus pentachloride, followed by filtration through silica gel and low temperature recrystallization.



(1)

	R^1	R^2	R^3	R^4	R^5	M.p. (°C)	N-I (°C) [a]
(a)	C_2H_5O	n-C_4H_9	H	H	H	137	—
(b)	C_2H_5O	n-C_4H_9	H	H	CH_3	49	44 [b]
(c)	C_2H_5O	n-C_4H_9	H	CH_3	H	60	60 [b]
(d)	C_2H_5O	n-C_4H_9	CH_3	H	H	64	59 [b]
(e)	C_2H_5O	n-C_4H_9	H	Cl	H	36	56
(f)	C_2H_5O	n-C_4H_9	Cl	H	H	29	58
(g)	C_2H_5O	n-C_8H_{17}	Cl	H	H	32	61
(h)	C_2H_5O	2-methylpentyl	Cl	H	H	32 [c]	41
(i)	C_2H_5O	2-methylhexyl	Cl	H	H	22 [c]	35
(j)	n-C_4H_9	n-C_8H_{17}	Cl	H	H	14	10 [b] −5 [b,d]
(k)	CH_3CO_2	n-C_4H_9	Cl	H	H	48	45 [b]
(l)	NC	n-C_4H_9	Cl	H	H	47	41 [b]

[a] Nematic-isotropic transition temperature.
[b] Monotropic transition.
[c] On cooling, the nematic phase is indefinitely stable at 18 °C.
[d] Smectic-nematic transition temperature.

Although additional corroborating experiments must be pursued, it can be tentatively concluded from the properties of the compounds shown in the table that our hypotheses are correct.

Two of the stilbenes, *(1h)* and *(1i)*, can be classified as room temperature nematic materials. Although the former substance is nematic at room temperature only in its supercooled state, neither has crystallized after several weeks at 18 °C, even in a thin film. The methyl branch may be detrimental to rapid crystallization. The stilbene *(1j)*, which is the only substance listed that contains two alkyl moieties as the wing groups, is a normal liquid at ambient temperatures and exhibits a smectic as well as a nematic phase.

Quite large enantiotropic nematic ranges are exhibited by *(1f)* and *(1g)*, and even longer ranges can be obtained by preparing binary mixtures. A formulation containing 60 mole-% *(1f)* and 40 mole-% *(1g)*, for example, has a nematic range of 8 to 59 °C.

All of the stilbene compounds *(2)* are white, crystalline solids at appropriate temperatures. The short wavelength cutoff of these materials is exemplified by the ultraviolet spectrum of stilbene *(1g)* in ethanol, $\lambda_{max} = 305$ nm ($\varepsilon = 28\,000$), $\lambda_{cutoff} = 350$ nm. Each one of the nematic phases observed as a colorless, turbid, mobile phase in a capillary tube could also be detected under a polarizing microscope equipped with a Mettler Hot/Cold Stage.

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Several of the compounds have been employed in their nematic states in the following experiments: the observation of dipole-dipole splitting in the nuclear magnetic resonance spectrum of a solute molecule dissolved in a nematic host[7,8]; the reproduction of the dynamic scattering effect, described by *Heilmeier* and co-workers[9], when suitable dopants are introduced into the cell[10]; the appearance of color bands, characteristic of a cholesteric mesophase, upon addition of cholesteric compounds to the mesomorphic stilbenes.

They are, in addition, potentially useful as stationary phases for gas chromatography[11] and as solvents in infrared[12], ultraviolet/visible[12], and ESR[13] spectrometric experiments.

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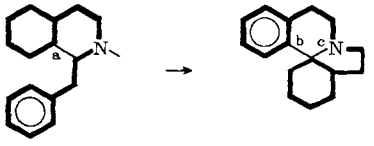
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Model Reactions for the Biosynthesis of Erythrina Alkaloids[1]

By *Burchard Franck* and *Volker Teetz*[*]

By feeding with radioactively labeled precursors *Barton et al.*[2,3] recently provided a proof that the skeleton of the Erythrina alkaloids (which have curare-like action) as well as that of morphine and other alkaloids is derived from a benzyltetrahydroisoquinoline *(1)*. The conversion of *(1)* into *(2)* must occur in three steps:



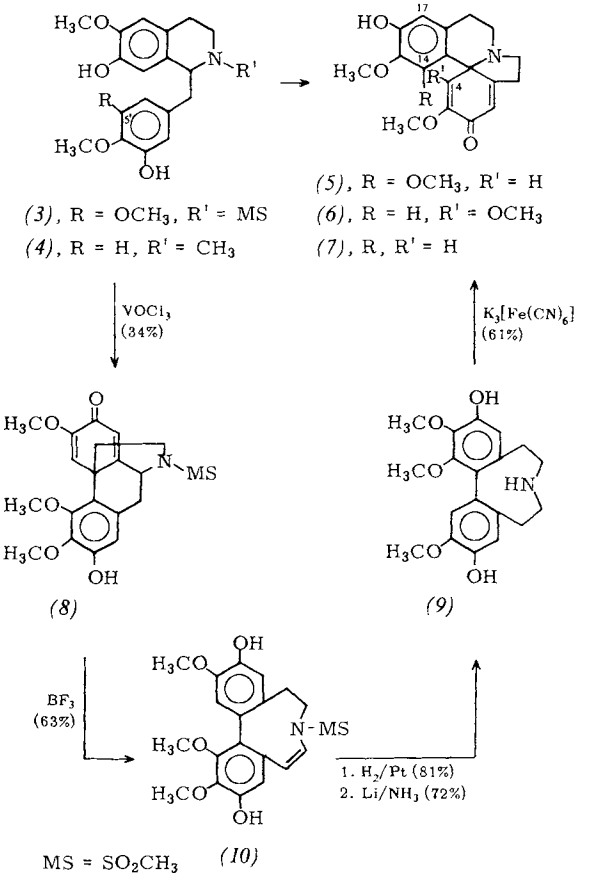
(1) *(2)*

1. Ring opening "a" in *(1)*;
2. Ring closure "b" in *(2)*;
3. Ring closure "c" in *(2)*.

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The third of these steps has already been clarified[3,4]. We now report on the preparative realization of this biogenetic scheme by synthesis of erythrinane *(5)* from the benzyltetrahydroisoquinoline *(3)*.

Oxidation of *N*-mesyl-5'-methoxynorreticuline *(3)* with $VOCl_3$[5] in CH_2Cl_2 gave the morphinandienone *(8)* in a yield of 34%, which is very high for an oxidative morphinan ring closure[6] [m.p. 235—238 °C; IR bands in KBr, 1665, 1640, 1615 cm^{-1} (dienone[7])] (ring closure b). Under very mild catalysis by BF_3/ether at 20 °C, which precludes an apomorphine rearrangement, *(8)* is rearranged to the isomeric biphenyl derivative *(10)* (ring opening a)[8]. This compound absorbs 1 mol of H_2 in presence of Pt/charcoal in methanol and in the NMR spectrum ($CDCl_3$, TMS = 10) shows three aromatic ($\tau = 3.60$, 3.45, and 3.14) and two *cis*-olefinic protons ($\tau = 4.63$ and 3.76; $J = 10.5$ Hz). Catalytic hydrogenation of *(10)* and subsequent demesylation by lithium in liquid NH_3 leads to the secondary amine *(9)* which can be condensed oxidatively by $K_3[Fe(CN)_6]$ in 5% $KHCO_3$ solution to give 14-methoxyerysodienone *(5)* (ring closure c). The structure of *(5)* is proved by the follow-



ing analytical findings: IR spectrum in KBr: 1680, 1655, and 1620 cm^{-1} (dienone[2,4]); NMR spectrum ($CDCl_3$, TMS = 10): $\tau = 4.28$, 3.79, and 3.77 (H on C-4, C-1, and C-17[2]); UV spectrum in methanol: $\lambda_{max} = 216$, 238, and 280 nm. These IR and UV data rule out the structure of the isomeric 4-methoxyerysodienone *(6)* which could have arisen by condensation of the nitrogen with the more highly substituted phenol portion.

The ready availability of the morphinandienone *(8)* (see below) is decisive for this new erythrinane synthesis with average yields of 60% per step. In view of these results norreticuline (*4*; R' = H) can be considered as biosynthetic

precursor for the Erythrina alkaloids that are derived from erysodienone *(7)*. It would first condense to the corresponding morphinandienone, whose *N*-methyl derivative, isosalutaridine[7] is found in Nature[10]; rearrangement analogous to *(8)* → *(10)* must then follow.

Morphinandienone (8):

Compound *(3)* (2.54 g) in anhydrous CH_2Cl_2 (2.5 l) was treated with $VOCl_3$[5] (2.4 g) in CH_2Cl_2 (120 ml) at −78 °C. and left at that temperature for 2 h. The mixture is then warmed to 20 °C, stirred for 2 h, washed with a saturated aqueous solution of Titriplex III (E. Merck), Na_2SO_4, and $KHCO_3$, and dried. The organic phase is evaporated and the residue is treated with warm ethyl acetate (20 ml), whereupon most of the morphinandienone *(8)* crystallizes. Further amounts of *(8)* can be obtained from the mother liquor by filtration through a short Al_2O_3 column (activity III) and elution of the leading zone. Total yield after recrystallization from CH_2Cl_2/ethyl acetate = 860 mg (34%).

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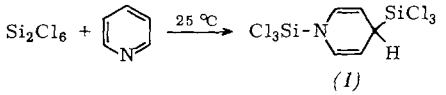
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1,4-Dihydro-1,4-bis-(trichlorosilyl)pyridine from Si_2Cl_6 and Pyridine[**]

By *D. Kummer* and *H. Köster*[*]

During our investigation of reactions of organic nitrogenous bases with Si—Si compounds[1,2] we have prepared a stable dihydropyridine derivative, namely, 1,4-dihydro-1,4-bis(trichlorosilyl)pyridine *(1)*.

The compound is formed when Si_2Cl_6 reacts with pyridine in the molar proportions 1:1 in benzene.



(1)

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^{1}H-NMR study of the course of the reaction shows that the 1,2-isomer is not formed as intermediate. Compound *(1)* can be separated in a state of purity by distillation of the reaction mixture. It is a colorless liquid that is stable in absence of air and moisture. The composition and structure are proved by the analytical findings: b.p. 69 °C/0.17 torr; ^{1}H-NMR (AA'LL'X type), $H_{2(6)}$ $\tau = 3.77$, $H_{(3,5)}$ $\tau = 5.24$, H_4 $\tau = 6.98$, $J_{2,3} = J_{5,6} = 8.2$ Hz; $J_{2,4} = J_{6,4} = 0.8$ Hz, $J_{4,3} = J_{4,5} = 4.4$ Hz (in CCl_4); mass spectrum, molecule ion at $m/e = 344.808$. This reaction provides a new route to stable 1,4-dihydro-1,4-bis(silyl)pyridines about which little is known[3]. NMR studies have shown that other halodisilanes such as Si_2F_6 and $Cl_2(CH_3)Si—Si(CH_3)Cl_2$ also react with pyridine to give dihydropyridine derivatives.

At the same time the reaction is a new type of base-catalyzed reactions of Si—Si compounds with organic nitrogenous bases. In previous reactions the disilane disproportionated to monosilane and oligosilane, this being followed in many cases by formation of the base adduct[4]. This disproportionation occurs also as side reaction in the 1:1 reaction. It becomes evident by appearance of a white insoluble adduct $SiCl_4 \cdot 2$ pyr and cannot be wholly suppressed in favor of formation of *(1)*. The yield of *(1)* is thus dependent on the reaction conditions.

Experimental:

A solution of pyridine (0.55 g, 7.0 mmol) in benzene (30 ml) is dropped with stirring into one of Si_2Cl_6 (1.90 g, 7.1 mmol) in benzene (30 ml) at 25 °C. The mixture becomes yellow and a small amount of a white precipitate of $SiCl_4 \cdot 2$ pyr is formed. After an hour the mixture is filtered, the benzene is condensed from the solution, and the residue is fractionated under reduced pressure. The yield is 0.96 g of *(1)*. All operations must be conducted with complete exclusion of air and moisture.

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Preparation of Tertiary Alkyl Azides

By *Paul Margaretha, Sonja Solar*, and *Oskar E. Polansky*[*]

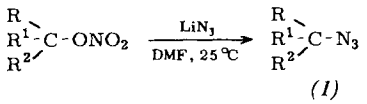
Very few syntheses of tertiary alkyl azides have been described in the literature[1]: *Pritzkow* and *Timm*[2] were able to obtain *tert*-butyl azide only in dilute cyclohexane solution; *Logothetis*[3] prepared 1,1-dimethyl-4-pentenyl azide from the corresponding alcohol and HN_3 in $CHCl_3$.

We have found a method that gives good yields of tertiary alkyl azides *(1)*, namely, treatment of alkyl nitrates with

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[**] Above 200 °C the reaction mixture is sensitive to shock and is a high explosive.

lithium azide in dimethylformamide at room temperature[**].



(1)

	R	R^1	R^2	Yield (%)
(a)	CH_3	CH_3	CH_3	75
(b)	CH_3	CH_3	C_2H_5	67
(c) [3]	CH_3	CH_3	$-(CH_2)_2CH=CH_2$	70

The structure of the products was proved by NMR, IR, and mass spectroscopy.

Experimental:

The alkyl nitrate (0.1 mol)[4] and lithium azide (0.15 mol)[5] are stirred in dimethylformamide (50 ml) for 8 h at room temperature. *(1a)*, b.p. 72 °C, is obtained by direct distillation of the solution; the other, higher-boiling azides are isolated as follows: dilution of the solution with water (1 l), extraction with ether (3 × 50 ml), and drying of the ether phase; *(1b)* is distilled at atmospheric pressure (b.p. 104 °C); *(1c)* is distilled in a vacuum (b.p. 22—25 °C/2 torr) since it isomerizes to the corresponding triazoline at higher temperatures[3].

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German version: Angew. Chem. *83*, 410 (1971)

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Structure of Ternary Copper(II) and Chromium(II) Fluorides

By *Hans Georg von Schnering, Bernhard Kolloch*, and *Alfons Kolodziejczyk*[*]

It was reported recently[1] that the structure of Sr_2CuF_6 involves square-planar and tetrahedral CuF_4 coordination but that structures of $SrCuF_4$, $CaCuF_4$, and $SrCrF_4$ involve only tetrahedral CuF_4 or CrF_4 coordination. This does not accord with results of our investigations of single crystals of Sr_2CuF_6 (greenish-blue), $SrCuF_4$ (bluish-green), $CaCuF_4$ (pale blue), and $BaCuF_4$ (colorless) that we obtained from melts (Pt crucibles) or by sintering (Ag bomb).

Sr_2CuF_6 crystallizes orthorhombically, and not tetragonally, in space group Bbam: $a=5.708(1)$, $b=5.708(1)$, $c=16.446(2)$ Å; $Z=2$. The symmetry could be established unequivocally. Atomic positions: Sr in 8(d) with $z=0.1621$, Cu in 4(b), F(1) in 8(e) with $x=0.2495$, F(2) in 16(g) with $x=0.6716$, $y=0.1749$, $z=0.0830$ ($R=9.5\%$ with 160 reflections *hkl*). The arrangement of Sr, Cu, and F(1) and the values of the F(2) parameters correspond with the data of *Hagenmuller et al.*[1], but, as a result of the change in symmetry, the Cu coordination found by us differs decisively from the reported value. Interatomic distances: Cu—F = 1.954 Å (4 ×), square planar; Sr—F = 2.469, 2.481, 2.484, 2.491 Å (each 2 ×), cubic.

$SrCuF_4$ and $CaCuF_4$ as well as $SrCrF_4$ crystals are of tetragonal $KBrF_4$ type, also with square-planar Cu(II) or Cr(II) coordination [$SrCuF_4$: $a=5.643(2)$, $c=10.672(5)$ Å; $CaCuF_4$: $a=5.377(2)$, $c=10.320(5)$ Å]. Here too the different findings of other authors[1] can be attributed to symmetry errors. Thus it was found for these three compounds that the X-ray intensities correspond to almost homometric pairs of structures, in which a decision between a tetrahedral and a square arrangement appears at first impossible, since the relative parameters of the F atoms depend on the zero point adopted for the metal lattice. However, the F parameter and thus the origin could be unambiguously established by the reflections *hkl* ($l=2n+1$). The compounds crystallize in the space group I4/mcm. Atomic positions: Sr, Ca in 4(a); Cu, Cr in 4(d); F in 16(l) with $x=0.1648$, $z=0.1230$ ($SrCuF_4$) or $x=0.1757$, $z=0.1281$ ($CaCuF_4$) or $x=0.1803$, $z=0.1240$ ($SrCrF_4$) ($R=6.6\%$, 6.2%, or 7.9%, respectively). Interatomic distances: Cu—F 1.858 or 1.880 Å (each 4 ×); Cr—F 1.980 Å (4 ×), Sr—F 2.506 or 2.496 Å (each 8 ×); Ca—F 2.349 Å (8 ×).

$BaCuF_4$, like $BaZnF_4$[2], is orthorhombic [$Cmc2_1$; $a=4.476$, $b=13.972$, $c=5.551$ Å; all atoms in 4(a) 0*yz* with (y; z) = Ba (0.1370; 0.000), Cu (0.4074; 0.0239), F_I (0.4812; 0.3365), F_{II} (0.3020; 0.2427), F_{III} (0.3291; −0.2454), F_{IV} (0.9321; 0.0350); with 440 reflections $R=8.1\%$]. However, a detailed consideration reveals distinct differences, particularly for the Cu—F distances [1.852, 1.872, 1.909, 2.018, and 2.265 (2 ×) Å]. The Ba atoms are surrounded by nine F atoms (Ba—F = 2.670 to 2.926 Å). In the structure of $BaCuF_4$ there is a (4 + 2) coordination whereas in the other fluorides the Cu atoms are bonded to only four F atoms. This possibly provides the reason for the differing colors. As shown by comparison with the analogous Ag(II) compounds[3], the $BaZnF_4$ type[2] and the Ba_2ZnF_6 type[4] are favored when the radii of the metals differ greatly; if this difference is small the $KBrF_4$ or Sr_2CuF_6 type is formed.

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German version: Angew. Chem. *83*, 440 (1971)

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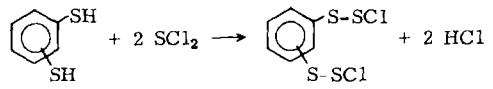
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Synthesis of Bis(chlorodisulfanyl)benzenes and Hexathia[3.3]cyclophanes[1]

By *Franz Fehér, Klaus Glinka*, and *Franz Malcharek*[*]

We recently reported the synthesis of bis(chlorosulfanyl)-benzenes[2] and reaction of the 1,2-isomer with geminal dithiols[1]. We have now obtained the three isomeric bis-(chlorodisulfanyl)benzenes *(4)* to *(6)* by reaction of the benzenedithiols *(1)* to *(3)* with an excess of dichloromonosulfane.

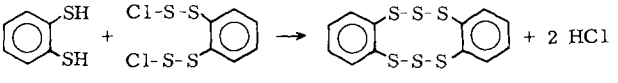
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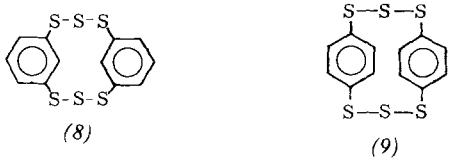
(1), *o* — *(4)*, *o*
(2), *m* — *(5)*, *m*
(3), *p* — *(6)*, *p*

Like the bis(chlorodisulfanyl)alkanes[3], the compounds *(4)* to *(6)* are obtained as orange-red oils that cannot be crystallized. The bis(chlorodisulfanyl)benzenes are stable at room temperature as pure substances and in solution. Satisfactory NMR and mass spectra could be determined for all three isomers. However, we were unable to obtain crystalline derivatives on treating *(4)* to *(6)* with piperidine, morpholine[2], or acetone[4].

When the dilution principle is applied, the bis(chlorodisulfanyl)benzenes react with the corresponding benzenedithiols to give the hexathia[3.3]cyclophanes. Hexathia[3.3]orthocyclophane *(7)* (dibenzo[*d*,*i*][1,2,3,6,7,8]hexathiocin) is thus formed from *(1)* and *(4)*, and we obtained hexathia[3.3]metacyclophane *(8)* and hexathia[3.3]paracyclophane *(9)* similarly as yellow crystals. All attempts to synthesize mixed hexathia[3.3]cyclophanes led to uncrystallizable oils with whose investigation we are currently occupied.

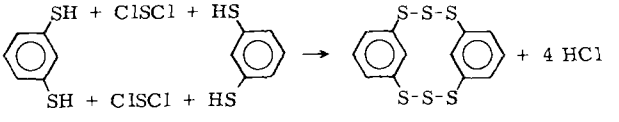


(1) *(4)* *(7)*



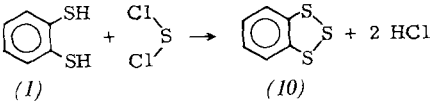
(8) *(9)*

Compounds *(8)* and *(9)* can also be obtained, but in poorer yield, by reaction of equimolar amounts of *(2)* or *(3)* with SCl_2. The corresponding reaction of *(1)* with



(2) *(2)* *(8)*

SCl_2 did not give the expected product *(7)*; only a viscous oil was isolated, which according to its mass spectrum has a molecular weight of 172[5]; it is probably trithia[3]orthocyclophane (1,2,3-benzotrithiole) *(10)*.



(1) *(10)*

Benzenedithiols:

The three isomeric benzenedisulfonyl chlorides can be converted into *(1)* to *(3)* by reduction with Zn/HCl[4, 6, 7]. This reaction can be effected appreciably more simply if red phosphorus and a catalytic amount of iodine in boiling glacial acetic acid are used as reducing agent[8]. *o*-Benzenedithiol *(1)* is, however, not obtainable in this new way, all attempts to do so giving only a solid polysulfide.

Bis(chlorodisulfanyl)benzenes:

A 0.005 M solution of *(1)* to *(3)* (0.71 g) in anhydrous carbon tetrachloride was dropped, with stirring, into freshly distilled dichloromonosulfane (70 ml) at −20°C, addition being complete in 15 min. The mixture is then allowed to come to room temperature and the volatile components are removed in a vacuum, leaving the products *(4)* to *(6)* as clear red oils in almost quantitative yield.

Hexathia[3.3]cyclophanes:

0.005 M solutions of *(4)* to *(6)* in CCl_4 (100 ml) and of *(1)* to *(3)* in diethyl ether (100 ml) are dropped separately but synchronously from two dropping funnels into ether (1.6 l) during 8 h. Removing the solvents then leaves *(7)* to *(9)* as crude products.

(8) and *(9)* can also be prepared by reaction of equimolar amounts of ethereal solutions of *(2)* and *(3)* with freshly distilled SCl_2 in ether in the above manner.

(7): flat yellow small rods from CS_2. Yield 57%. Softens at 160°C. Mol. wt. (mass-spectrographic) 344.

(8): yellow needles from ether. Yield 51% (15% by the second method). M.p. 116°C. Mol. wt. (mass-spectrographic) 344.

(9): small yellow leaflets from CH_2Cl_2. Yield 42% (6%). Softens at 150°C. Mol. wt. (mass-spectrographic) 344.

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[8] *A. W. Wagner*, Chem. Ber. *99*, 375 (1966).

Structure of the Red Eye Pigments of the Fruit Fly *Drosophila melanogaster*[**]

By *Heinrich Schlobach* and *Wolfgang Pfleiderer*[*]

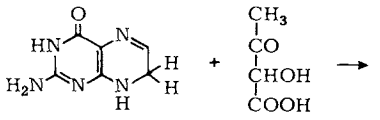
Viscontini et al.[1] reported the separation, from *Drosophila* eyes, of the red pigment fraction that absorbs at about 500 nm and made several proposals for the constitutions of the three components, drosopterin *(3)*, isodrosopterin *(4)*, and neodrosopterin. Since none of the monomeric dihydropterin structures postulated could explain the long-wave absorption, the relatively small R_F values, or the unusually high optical rotations of drosopterin and isodrosopterin, we suggested, in 1963, that these pigments might be dipteridinyl derivatives[2].

Starting from an observation by *Forrest*[3], we have found that reaction of 7,8-dihydropterin *(1)* and 2-hydroxy-3-

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

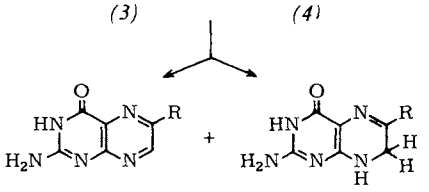
oxobutyric acid *(2)* gives a 70% yield of a mixture of *(3)* and *(4)*, both of which we obtained pure in 10% yield by one separation on a cellulose column. UV, ORD, CD, and fluorescence spectra, as well as chromatographic and electrophoretic comparison, revealed no difference between the natural and the synthetic materials.



(1) *(2)*

Drosopterin + Isodrosopterin

(3) *(4)*



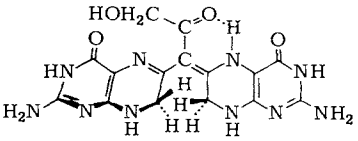
(5), R = OH *(9)*, R = OH
(6), R = NH_2 *(10)*, R = CO_2H
(7), R = H
(8), R = CO_2H

Molecular-weight determinations in an ultracentrifuge gave values around 430±5%, as were found also by *Sugiura* and *Goto*[4]. Spectral comparison with dimeric xanthopterin derivatives had led first[5] to constitutions involving direct C—C linkage of two pterin rings at the 7 positions, but such structures were ruled out by the products obtained on alkaline hydrolysis of *(3)* and *(4)*. On treatment with 1% ammonia solution drosopterin and isodrosopterin gave a large number of hydrolysis products, among which xanthopterin *(5)*, 6-aminopterin *(6)*, pterin *(7)*, pterin-6-carboxylic acid *(8)*, 7,8-dihydroxanthopterin *(9)*, and 7,8-dihydropterin-6-carboxylic acid *(10)* could be identified by chromatographic comparisons and by determination of remission spectra. In addition, a yellow-fluorescing degradation product was found whose UV spectrum was related to that of sepiapterin[6]. 0.1 N NaOH or 4% Na_2CO_3 solution degraded *(3)* and *(4)* to the same products, except for *(6)*.

Elemental analyses of crystalline drosopterin and isodrosopterin gave molecular formulas $C_{15}H_{20}N_{10}O_6$ which, according to NMR spectra, must refer to stable dihydrates of the molecule $C_{15}H_{16}N_{10}O_4$; however, we have not yet succeeded in effecting dehydration without decomposition. NMR spectra of *(3)* and *(4)* are not very informative and are difficult to interpret, but from the spectra in [D_6]DMSO, CF_3COOH, and conc. H_2SO_4 it can be deduced that no methyl or methine group is present. Catalytic hydrogenation of *(3)* and *(4)* with Pt/H_2 causes decoloration and absorption of 2 equivalents of hydrogen, yielding products that have UV spectra characteristic of 5,6,7,8-tetrahydropterins[7].

The synthesis of drosopterin and isodrosopterin certainly involve a two-fold *Michael* addition of the methyl group of 2-hydroxy-3-oxobutyric acid to the azomethine function of *(1)* since the latter is readily accessible to nucleophilic attack[8], and this is followed by dehydrogenation and decarboxylation. This synthetic pathway together with the facts given above strongly suggest structure *(11)*.

Compounds *(3)* and *(4)* are not merely isomeric, but, contrary to earlier suppositions[9], are clearly shown to be enantiomers by the ORD[10] and CD spectra, which are symmetrical about the zero line. The very large optical activities of the two optical antipodes are due to an inherent-



(11)

ly dissymmetric chromophore, which in turn results from non-planarity of the two 7,8-dihydropterin rings caused by steric hindrance. The hindrance to free rotation around the C—C single bond at positions 6 is, as shown by a model, due mainly to the neighboring methylene groups, and the steric effects are so great that it has not yet been possible to interconvert *(3)* and *(4)* by thermal isomerization. So far as we know, the red eye pigments drosopterin and isodrosopterin thus constitute a new class of atropisomeric natural pigments.

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Monothioformic Acid[1]

By *Gerhard Gattow* and *Rudolf Engler*[*]

The existence of monothioformic acid HCOSH has been signaled in the literature[2].—The free acid is formed on treatment of Na[HCOS] or K[HCOS] (prepared by hydrolysis of phenyl formate with NaHS or KHS) with 18% HCl and it can be distilled from the solution in a vacuum at −5 °C.

The pale yellowish acid (m.p. −68 °±1 °C, $d_4^{20}=1.34\pm0.02$ g/ml, $n_D^{20}=1.4880\pm0.0005$, $K_a=9\times10^{-3}$ in H_2O), which polymerizes to $[HCOSH]_x$ even at 30 °C, is very readily soluble in $CHCl_3$ and CH_2Cl_2 but less so in water. $[HCOSH]_x$ dissolves almost only in aqueous sodium hydroxide and then with partial disproportionation to $[HCO_2]^-$ and $[HCS_2]^-$[3]. In the mass spectrum of $[HCOSH]_x$ there appear, besides the molecular ion at $m/e=62$, the disproportionation products at $m/e=46$ (HCOOH) and 78 (HCSSH)[4] in the ratio 1:1, together with small amounts of $[HCOSH]_2$ but no trimeric unit[4].

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Aqueous solutions of the $[HCOS]^-$ ion and of the monomeric acid show visible and UV absorptions at 211 and 247 nm and additionally at 223 nm respectively. The ^{1}H-NMR spectrum[5] of HCOSH contains two singlets at $\delta_{C-H}=10.18$ and $\delta_{S-H}=4.66$ ppm. The singlet in the ^{1}H-NMR spectrum of the $[HCOS]^-$ ion [measured in D_2O against sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate] at $\delta=10.64$ ppm fits well into the series of ions $[HCOO]^-$ at $\delta=8.42$ ppm and $[HCSS]^-$ at $\delta=12.22$ ppm[3].

IR spectrum of $[HCOS]^-$: 2810 (m), 1610 (m), 1525 (s), 1352 (m), 946 (m), 844 (s) cm^{-1}[6]. IR spectrum of HCOSH: 3310 (w), 2850 (m), 2540 (m), 1661 (s), 1339 (m), 1235 (w), 1160 (w), 1055 (w), 946 (s), 727 (s), 692 (s), and 666 (s) cm^{-1}[6].

From the UV and ^{1}H-NMR spectra it can be seen that HCOSH exists preferentially in the thiol form; only the weak bands in the IR spectrum at 3310 (O—H) and 1235 (C=S) cm^{-1} indicate very small amounts of acid in the hydroxy form. This is in accord with results obtained in the study of monothioacetic acid[7].

Both *S*- and *O*-esters of HCOSH can be prepared: the *S*-methyl ester is formed on reaction of Na[HCOS] with methyl iodide, and the *O*-ester on reaction of methyl orthoformate and H_2S in the presence of $ZnCl_2$ and hydroquinone[8]. ^{1}H-NMR spectrum of $HCO(SCH_3)$: $\delta_{CH}=10.12$ and $\delta_{CH_3}=2.34$ ppm; of $HCS(OCH_3)$: $\delta_{CH}=9.66$ and $\delta_{CH_3}=4.02$ ppm.

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[5] 60 MHz; measured in $DCCl_3$ against TMS as internal standard.

[6] s = strong, m = medium, w = weak.

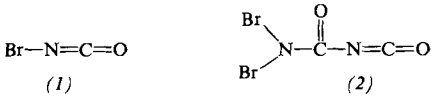
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Bromine Isocyanate

By *Waldemar Gottardi*[*]

Birckenbach and *Linhard*[1] failed to obtain bromine isocyanate *(1)* by treating silver isocyanate with bromine in ethyl chloride at −80 °C, obtaining instead the acyclic dimer, *N,N*-dibromocarbamoyl isocyanate *(2)*.



(1)

(2)

Since monomeric chlorine isocyanate[2] and iodine isocyanate[3] can be prepared it appeared that it should be possible to synthesize *(1)* if the reaction conditions were chosen so as largely to exclude dimerization. This can be done by reaction of gaseous Br_2 with AgNCO at 150 °C and condensation of the resulting *(1)* at −196 °C.

$$Br_2 + AgNCO \xrightarrow[1\ torr]{150\,^\circ C} (1) + AgBr$$

Carbonyl isocyanate is formed as by-product, in proportions increasing as the temperature is raised; at 250 °C it is the main product.

Bromine isocyanate in the solid state (below −60 °C) forms yellow crystals that melt to a brown unstable liquid that dimerizes to crystalline *(2)* very rapidly. In this, *(1)* differs from chlorine isocyanate which dimerizes under these conditions to the cyclic 1,3-dichlorouretidinedione[4]. *(1)* is characterized, not only by this ready polymerization but also by extreme sensitivity to moisture; the cyanic acid formed on hydrolysis can be detected by IR spectroscopy. Purification of *(1)* is accompanied by great losses because its volatility is comparable with that of cyanic acid and of bromine $[HCNO \geqslant (1) \geqslant Br_2]$ and because liquid *(1)* is unstable, so that *(1)* has in fact not been obtained completely free from bromine.

The IR spectrum of *(1)* (condensed on a KBr disk cooled in liquid N_2) showed bands in the 4000—400 cm^{-1} region at 3440 m, 2256 s, 2164 vs, 2120 ms, 1289 ms, 690 ms, 566 s, and 473 m cm^{-1}. Molecular weight (mass-spectrometric): 122.

Experimental:

A column (length 15 cm, ∅ 2 cm) of a finely ground (24 h) mixture of AgNCO (prepared according to[5]; 40 g) and roasted quartz powder (20 g) is pre-heated for 12 h at 200 °C; gaseous bromine (taken from a trap cooled at −45 °C) is passed at 1 torr in a dynamic vacuum through this column while it is heated at 150 °C. The reaction products are condensed at −196 °C. *(1)* can be largely purified by several fractional recondensations in the temperature range −45 to −85 °C.

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Trisboranephosphite and Tetrakisboranephosphate Ions

By *Erwin Mayer*[*]

Oxyacids of non-metals and their ions show a surprising chemical resemblance to compounds in which the oxygen is replaced by an isoelectronic BH_3 group[1]. Boranecarbonyl, H_3BCO, and the boranecarbonate ion, $[H_3BCO_2]^{2-}$, react similarly to CO_2 and CO_3^{2-}. Of the analogs of phosphorus-oxygen ions, the bisboranephosphite ion *(1)* which is isoelectronic with hypophosphite is already known[2–4]:

$$H_3P \cdot BH_3 + BH_4^- \longrightarrow [H_2P(BH_3)_2]^- + H_2$$

(1)

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The two hydrogen atoms of *(1)* that are bonded to phosphorus react no further with BH_4^- because of their low acidity. Stepwise removal of both these protons is, however, possible by reaction of *(1)* with *n*-butyllithium; trisboranephosphite *(2)* and tetrakisboranephosphate *(3)*, which are isoelectronic with, respectively, phosphite and phosphate, are then formed by subsequent addition of diborane:

$$[H_2P(BH_3)_2]Li + n\text{-}C_4H_9Li + 0.5\ B_2H_6 \rightarrow [HP(BH_3)_3]Li_2 + C_4H_{10}$$
(2)

$$[HP(BH_3)_3]Li_2 + n\text{-}C_4H_9Li + 0.5\ B_2H_6 \rightarrow [P(BH_3)_4]Li_3 + C_4H_{10}$$
(3)

The reaction must be carried out stepwise: adding first 2 mol of *n*-butyllithium per mol of $[H_2P(BH_3)_2]Li$ and then adding one mol of diborane does not lead to formation of *(3)*.

The compounds *(2)* and *(3)* are sparingly soluble in diethyl ether but soluble in dimethoxyethane and in acetonitrile; thus the $LiBH_4$ formed as by-product can be separated by extraction with ether.

Compounds *(2)* and *(3)* are crystalline salts that dissolve in water without decomposition and are oxidized by air. Solvated salts crystallize from concentrated solutions in dimethoxyethane.

Compound *(2)* was isolated in a pure state and was characterized by analysis and by its ^{1}H-NMR spectrum, but *(3)* was obtained only together with *(2)* and $LiBH_4$ as impurities.

The ^{1}H-NMR spectrum of *(2)* in D_2O consists of two groups of signals. A 1:1:1:1 quartet at $\tau = 9.57$ is formed by coupling of the BH_3 protons with ^{11}B ($J_{B-H} = 86$ Hz). A doublet at $\tau = 8.18$ is formed by coupling of the PH proton with ^{31}P ($J_{P-H} = 274$ Hz). The two doublet components are further split, by coupling with the nine equivalent protons bonded to boron, into a decet with the expected intensities ($J_{H-H} = 6$ Hz). The ^{1}H-NMR spectrum of *(3)* consists of a 1:1:1:1 quartet at $\tau = 9.58$ ($J_{B-H} = 86$ Hz).

In the series $H_3P \cdot BH_3$, $[H_2P(BH_3)_2]^-$, $[HP(BH_3)_3]^{2-}$ the increasing negative charge on the complex causes increased shielding of the protons bonded to phosphorus ($\tau = 5.69$[5], 6.90[6], and 8.18, respectively). However, the chemical shifts of the BH_3 protons alter only slightly: $\tau = 9.47$[5], 9.57[6], 9.57, and 9.58, respectively, for $H_3P \cdot BH_3$, $[H_2P(BH_3)_2]^-$, $[HP(BH_3)_3]^{2-}$, and $[P(BH_3)_4]^{3-}$.

Experimental:

$[HP(BH_3)_3]Li_2$: $[H_2P(BH_3)_2]Li$ (8.17 mmol) was dissolved in ether and treated at −196 °C with an equivalent amount of *n*-butyllithium, then allowed to warm to room temperature and stirred for 2 h. A white precipitate was formed. Then B_2H_6 (4.08 mmol) was condensed in at −196 °C. After this mixture had warmed to room temperature the solvent was pumped off and the residue was washed several times with diethyl ether, after which the $[HP(BH_3)_3]Li_2$ was extracted with dimethoxyethane; the yield was 46% (3.79 mmol). The salt melts at 200 °C with slow evolution of hydrogen.

$[P(BH_3)_4]Li_3$: Preparation and working up were as for $[HP(BH_3)_3]Li_2$, but $[HP(BH_3)_3]Li_2$ was used as starting material. The yield was 37%. All the reactions were carried out with exclusion of oxygen.

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Hexacyclo[4.4.0.0^{2,4}.0^{3,9}.0^{5,7}.0^{8,10}]decane, a Bridged *cis*-Trishomobenzene

By *Armin de Meijere*, *Dieter Kaufmann*, and *Otto Schallner*[*]

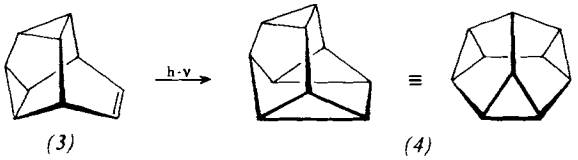
The importance of homoconjugation within the concept of homoaromaticity[1] has recently been demonstrated for *cis,cis,cis*-1,4,7-cyclononatriene *(1)*[2].


(1)


(2)

The valence tautomer of this molecule, a trishomobenzene *(2)* which arises formally by cyclopropanation of the three double bonds of benzene, has not yet been prepared[3]. We now report a synthesis of the hydrocarbon *(4)* which has the structural characteristics of *(2)*[4].

Irradiation studies with the two isomeric bishomobarrelenes[5] have shown that it is the *anti*-isomer that preferentially undergoes photochemical rearrangement[6], and this finding accords with results in the homobornadiene system[7]. By analogy it was to be expected that on irradiation of the bridged bishomobarrelene *(3)*[8] a rearrangement would occur which could lead to the hydrocarbon *(4)*.



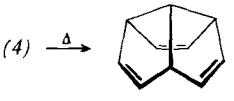
(3) *(4)*

Compound *(3)* was therefore irradiated at −10 °C in pentane under nitrogen for 48 h[9]. Following the progress of the reaction by gas chromatography showed that after this time some 70% of the starting material had reacted. The reaction mixture contained, besides *(3)* (53%) and three as yet unidentified components (together *ca.* 17%), a 30% yield (by gas chromatography) of a compound which according to its mass spectrum had a molecular weight of 130[10].

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This product could be obtained pure (isolated yield *ca.* 5%) by preparative gas chromatography under mild conditions. Its ^{1}H-NMR spectrum (100 MHz, CCl_4) showed it to have the structure of a hexacyclo-[4.4.0.0^{2,4}.0^{3,9}.0^{5,7}.0^{8,10}]decane *(4)*. The spectrum contained three signals in the intensity ratio 3:1:6 [$\tau = 7.16$ (m, 3H), $\tau = 7.42$ (m, 1H), $\tau = 8.37$ (m, 6H)]. The neighborhood relationship of the three types of protons was proved by double resonance experiments: irradiation at $\tau = 7.16$ converted the signal at $\tau = 8.37$ into a singlet, and irradiation at $\tau = 8.37$ converted the signal at $\tau = 7.16$ into a singlet and that at $\tau = 7.42$ into a quadruplet. The molecular formula $C_{10}H_{10}$ was confirmed by high-resolution mass spectrometry. The IR spectrum is in accord with the proposed structure (point group C_{3v}). The compound shows only end absorption in its UV spectrum.

'Diademane' *(4)* forms highly volatile, colorless crystals melting at 96–97 °C (with rearrangement). When warmed it rearranges smoothly to triquinacene *(5)*[11] (half-reaction time *ca.* 60 min at 90 °C), which was identified by means of its characteristic ^{1}H-NMR spectrum. This $-[_\pi 2_s + _\pi 2_s + _\pi 2_s]$-cycloreversion, which is an allowed con-



(5)

certed process according to the principle of conservation of orbital symmetry[12], is perhaps here made extra easy by the considerable ring strain which, according to models, appears to be present in the molecule.

Attempts to determine this strain energy and to study the electronic interaction between the three cyclopropane rings of *(4)* by means of photoelectron spectroscopy are in progress.

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Trifluoroarsine as Ligand for a Complex [**]

By *Jörn Müller* and *Klaus Fenderl* [*]

Trifluorophosphine forms many stable complexes with transition metals in their lower oxidation states[1], but the only arsenic trihalide complexes described previously are the trichloro compounds $Mo(CO)_{6-n}(AsCl_3)_n$ where $n = 1$ to 3[2,3].

We now report the preparation of the first trifluoroarsine complex *(1)*, by ligand exchange, starting from the cycloheptene compound $C_5H_5Mn(CO)_2C_7H_{12}$ which has been described as very labile[4].

$$C_5H_5Mn(CO)_2C_7H_{12} + AsF_3 \xrightarrow[3h]{C_6H_6,\ 55\,^\circ C} C_5H_5Mn(CO)_2AsF_3 + C_7H_{12}$$

(1)

After removal of the solvent, excess of AsF_3, and liberated cycloheptene, dicarbonylcyclopentadienyl(trifluoroarsine)-manganese(I) *(1)* was isolated as yellow crystals in 30 to 40% yield by sublimation in a vacuum at 20 °C (m.p. 64 °C, dec.). The compound is very sensitive to hydrolysis and not particularly stable thermally. It is formed also by UV irradiation of a benzene solution of $C_5H_5Mn(CO)_3$ *(2)* in presence of AsF_3, but separation of *(1)* and *(2)* did not prove possible.

In the mass spectrum (50 eV) of *(1)* the following characteristic fragments appeared alongside the molecular ion $C_5H_5Mn(CO)_2AsF_3^+$ ($I_{rel.} = 6.3$): $C_5H_5Mn(CO)_2AsF_2^+$ (0.6), $C_5H_5Mn(CO)AsF_3^+$ (1.7), $C_5H_5Mn(CO)AsF_2^+$ (2.5), $C_5H_5MnAsF_3^+$ (5.7), $C_5H_5MnAsF_2^+$ (3.7), $C_5H_5Mn(CO)_2^+$ (7.8), $C_5H_5MnCO^+$ (18), $C_5H_5Mn^+$ (78), MnF^+ (5.4), and Mn^+ (100). The relatively high intensities of the $C_5H_5Mn(CO)_n^+$ ions indicate that AsF_3 must be similar to CO ligands in its donor-acceptor strength[5].

The symmetrical AsF stretching vibration of complexed AsF_3 lies at 694 cm^{-1} (KBr disk); it is shifted by only 11 cm^{-1} towards longer wavelengths relative to its position for the free ligand.

Table 1. Spectroscopic properties of the AsF_3 and PF_3 complexes *(1)* and *(3)*.

	ν_{CO} (cm^{-1})	k_{CO} (mdyn/A)	$\tau_{C_5H_5}$	*IP* (eV)
(1)	2006 1953	15.83	4.90	8.34
(3)	1996 1938	15.63	5.02	8.24

To obtain more information on the donor-acceptor behavior of AsF_3 ligands we have compared a few spectroscopic properties of *(1)* with those of the PF_3 complex $C_5H_5Mn(CO)_2PF_3$ *(3)*[5]. Table 1 contains the ν_{CO} vibrations (*n*-hexane) and CO valence force constants (calculated according to [6]), as well as the chemical shifts of the ^{1}H-NMR signals of the C_5H_5 ligands (measured in deuterioacetone) and the ionization potentials (measured by the electron impact method), for *(1)* and *(3)*. The values show that the electron density on the central Mn atom is lower in *(1)* than in *(3)*. Thence it follows that AsF_3 has an elec-

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tron-attracting action still more powerful than that of the already powerful acceptor PF_3.

This remarkable property can be ascribed at least in part to the weaker donor character of AsF_3 than of PF_3 ligands. The ionization potentials measured by us amount to 11.7 eV for PF_3 and 12.8 eV for AsF_3; the lone pair involved in the ionization thus lies at a lower energy level in the case of AsF_3.

The fluorine atoms in *(1)* can be very readily exchanged in nucleophilic reactions, even at room temperature, without simultaneous attack on the Mn—As bond. If a benzene solution of *(1)* is treated with ethanol at 20 °C, a very rapid reaction affords

$C_5H_5Mn(CO)_2AsF_2OC_2H_5$

together with a small amount of

$C_5H_5Mn(CO)_2AsF(OC_2H_5)_2$

The PF_3 complex is inert under these conditions.

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New Method of Preparing Iminosulfur Oxydifluorides

By *Wolfgang Sundermeyer, Achim Roland*, and *Konrad Seppelt*[*]

It is not always possible to prepare a desired iminosulfur oxydifluoride by the method most used hitherto[1], namely, reaction of an NH_2 group with sulfur oxide tetrafluoride. This is due, not only to the relatively great stability of OSF_4, but also to the facts that the relevant amines in part do not react and in part do not exist, the latter particularly in those cases where two or more NH_2 groups should be attached to one atom. As a result, compounds containing more than one $NS(O)F_2$ group attached to one atom are accessible only by special reactions and indeed are known only in three cases, namely, $F_2C(NSOF_2)_2$, $OC(NSOF_2)_2$[2], and mercury bis(iminosulfur oxydifluoride), $Hg(NSOF_2)_2$ *(1)*[3].

Synthesis of the last-mentioned compound and its reactions with polar halides have now provided a method of introducing the $NSOF_2$ group, by means of which a large number of new iminosulfur oxydifluorides can be prepared. For instance, phosphorus trichloride reacts with *(1)* in methylene chloride to give phosphorus tris(iminosulfur oxydifluoride) *(2)*.

$$3\ \underset{(1)}{Hg(NSOF_2)_2} + 2\ PCl_3 \rightarrow 2\ \underset{(2)}{P(NSOF_2)_3} + 3\ HgCl_2$$

Similarly, arsenic tris(iminosulfur oxydifluoride), $As(NSOF_2)_3$ *(3)*, is obtained from arsenic trichloride, and silicon tetrachloride can be converted into silicon tetrakis(iminosulfur oxydifluoride) *(4)*, which is to date the most highly substituted compound of this type.

$$2\ \underset{(1)}{Hg(NSOF_2)_2} + SiCl_4 \rightarrow \underset{(4)}{Si(NSOF_2)_4} + 2\ HgCl_2$$

It is evident that alkyl- and aryl-substituted inorganic halides can be subjected to this reaction. For example, all the members of the series $(CH_3)_xSi(NSOF_2)_{4-x}$ have been prepared [*(4a)* to *(4c)*], and it could thus be shown that compounds with more than two $NSOF_2$ groups are also stable, although the Si—N bond itself usually reacts with S—F compounds.

The most interesting example so far of an iminosulfur oxydifluoride of a Group 6 B element is thionyl bis(iminosulfur oxydifluoride) *(5)* which is formed by the reaction of *(1)* with thionyl chloride. Analysis and the mass spec-

Table 1. Properties of some iminosulfur oxydifluorides.

Compound	Yield (%)	M. p. (°C)	B. p. (°C/torr)	^{19}F-NMR (ppm) [a]	IR spectra (cm^{-1}) [c] vSO	vSN	ν_{as}SF	ν_sSF	Other bands
$P(NSOF_2)_3$ *(2)*	50	−21.5	48.5/12	−51.7 D [b]	1415 s, br	1238 s	840 s		690, 615, 547, 509, 453, 360
$As(NSOF_2)_3$ *(3)*	40	− 3	38/0.4	−54.9 S	1515–1400 s	1215 s	820 s	760 m	645, 618, 550, 505, 430, 320
$Si(NSOF_2)_4$ *(4)*	30	−39	61/13	−48.4 S	1481–66 s	1308 s	905 s	866 s	737, 641, 608, 550, 485, 460
$RSi(NSOF_2)_3$ *(4a)*	40	−65	47/12	−49.6 S	1460 s, br	1295 s	900 m	852 s	2982 νCH, 791 γCH_3, 772, 705, 550, 520, 467
$R_2Si(NSOF_2)_2$ *(4b)*	84	−86	24/10	−50.6 S	1455 s, br	1289 s	880 s	832 s	2975 ν_{as}CH, 2940 ν_sCH, 801 γCH, 710, 552, 520, 455
$R_3Si(NSOF_2)$ *(4c)*	85	−92	85.5/760	−55.9 S	1495 s, br	1275 s	852 s	819 s	(cf. [3])
$OS(NSOF_2)_2$ *(5)*	50		56/30	−51.7 D	1415 s 1234 s	1166 s	865 s	845 m	690, 650, 560, 515, 450

[a] 24 °C, $CFCl_3$ as external standard. S = singlet, D = doublet.
[b] J_{P-F} = 4.5 Hz; ^{31}P-NMR: δ = −84.5 ppm, H_3PO_4 as external standard.
[c] *(2)* and *(3)* as film, all others as gases. Provisional assignments.

trum lead to the conclusion that this is a homogeneous substance, but spectroscopic findings, in particular the ^{19}F-NMR spectrum, indicate the presence of isomers.

$$Hg(NSOF_2)_2 + OSCl_2 \rightarrow OS(NSOF_2)_2 + HgCl_2$$
(1) *(5)*

Experimental:

The imide *(1)* (15 g) is suspended in methylene chloride (*ca.* 50 ml; partially dissolved; 5 g/100 ml), treated with the appropriate inorganic halide [slight excess of *(1)*; if necessary, diluted with CH_2Cl_2), and heated under reflux for 5—10 h. The products are obtained analytically pure by fractional distillation in a vacuum.

All the products are water-clear liquids of unexpectedly high stability and low sensitivity to hydrolysis. Boiling points are similar to those of the corresponding bromides (differences *ca.* +7 °C per $NSOF_2$ group). Physical data of the products, whose structures are proved by elemental analysis and by mass spectra, are shown in Table 1[4].

As we have also shown in previous experiments[3, 5], the OSN, F_2SN, and $F_2S(O)N$ groups can be regarded as resembling pseudohalides although the corresponding anions have not yet been isolated—but we have obtained all the *N*-haloiminosulfur oxydifluorides $XNSOF_2$ (X = F, Cl[6], Br, and I[7]). If this view is accepted, compound *(5)* is the first stable thionyl pseudohalide (cf. [8]).

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CONFERENCE REPORTS

Porous Plastic Foils as Functional Models of Excitable Nerve Membranes

By *U. F. Franck* and *S. Searty*[*]

Membranes are among the most important functional building units of living organisms, where they undertake physicochemical processes that are essential for life. Such processes are, above all:

a) separation of materials;
b) energy transfer;
c) transfer and processing of information.

In spite of the variety of these processes they can be referred in principle to two elementary properties of membranes, namely:

a) selectivity with respect to permeability;
b) capability to couple in all the processes that can occur in the neighborhood of the membrane.

Selectivity leads to effects such as electric potentials, mechanical pressure *etc.* On the other hand, coupling mechanisms enable membranes to exhibit excitability, rhythmic behavior, and propagation phenomena.

Such phenomena play an important part in rapid transfer of information in nerves, muscles, and sensorial organs.

Coupling mechanisms of this kind are observed also with non-living membranes, *e. g.*, with porous plastic foils (PVC, polystyrene, *etc.*). The kinetic behavior of such membranes, which contain traces of fixed ions in their pores, is analogous to that of excitable nerve membranes, and all the fundamental electrophysiological properties such as excitability, accommodation, action potential, and rhythmic behavior can be demonstrated with these materials.

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Mechanism of the Radiolysis of Cyclohexane

By *Horst Herler*[*]

Cyclohexane is very useful in studying reactions that are initiated by ionizing radiation since it contains only one kind each of C—C and C—H bonds. The three main products—hydrogen, cyclohexene (C_6H_{10}), and bicyclohexane ($C_{12}H_{22}$)—are formed by rupture of C—H bonds. Absorption of ionizing radiation leads to excited and ionized cyclohexane molecules and to electrons. Experimental results and theoretical considerations both indicate that most of these electrons are thermalized whilst still in the Coulomb field of their parent ion. A few electrons, however, have sufficient energy to escape from the parent ion, the number of these amounting to *ca.* 0.10 electron per 100 eV. The lifetime of ions and electrons up to their recombina-

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tion is important for the possibility of ion-molecule reactions. According to *Freeman* and *Fayadh*[1] recombination occurs in $10^{-10\pm1}$ s.

The amounts of the main products of radiolysis of cyclohexane are increased by addition of small quantities of organic compounds such as benzene, anthracene, and pyrene; the amounts of all three products are maximal at *ca.* 10^{-4} mole of aromatic compound per liter.

$$C_6H_{12} \rightsquigarrow C_6H_{12}^+ + e^- \quad (1)$$

$$C_6H_{12} \rightsquigarrow C_6H_{12}^* \quad (2)$$

$$C_6H_{12}^+ + e^- \rightarrow C_6H_{12}^* \quad (3)$$

$$C_6H_{12}^* \rightarrow C_6H_{10} + H_2 \quad (G \approx 1.2) \quad (4)$$

$$C_6H_{12}^* \rightarrow C_6H_{11}^\cdot + H_{kin}^\cdot \quad (5a)$$

$$H_{kin}^\cdot + C_6H_{12} \rightarrow C_6H_{11}^\cdot + H_2 \quad (5b)$$

$$C_6H_{12}^+ + C_6H_{12} \rightarrow C_6H_{13}^+ + C_6H_{11}^\cdot \quad (6a)$$

$$C_6H_{13}^+ + e^- \rightarrow C_6H_{11}^\cdot + H_2 \quad (6b)$$

$$C_6H_{12}^+ + C_6H_{12} \rightarrow C_{12}H_{22}^+ + H_2 \quad (7)$$

$$C_{12}H_{22}^+ + e^- \xrightarrow{M} C_{12}H_{22} \quad (8)$$

$$C_6H_{12}^* \rightarrow C_6H_{11}^\cdot + H_{th}^\cdot \quad (G \approx 1.5) \quad (9)$$

$$C_6H_{11}^\cdot + C_6H_{11}^\cdot \rightarrow C_6H_{10} + C_6H_{12} \quad (G \approx 1.8) \quad (10)$$

$$C_6H_{11}^\cdot + C_6H_{11}^\cdot \rightarrow C_{12}H_{22} \quad (G \approx 1.8) \quad (11)$$

Aromatic compounds can scavenge electrons and species having a positive charge; in such reactions, the mobility of electrons may make attachment of electrons more effective than charge transfer, and this increases the lifetime of cyclohexane radical cations. As a result, product formation by ion-molecule reactions should have greater importance, since the efficiency of product formation by ion-molecule reactions is greater. Indications of this in the case of cyclohexane are provided by investigations with electron scavengers, for the probability of ion-electron recombination is about 0.7 if that for ion-molecule reactions is set = 1.

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Electrolytic Reduction of Higher Metal Halides in Methanol

By *H.-J. Seifert*[*]

VCl_3 can be reduced electrolytically in methanolic solution exactly as in an aqueous medium. Green $VCl_2 \cdot 2CH_3OH$ can be isolated on concentration of the violet solution of V^{2+}. Treatment with organic complexing reagents such as pyridine, acetonitrile, tetrahydrofuran (THF), dimethylformamide (THF), *etc.*, permits preparation of complexes containing these ligands with removal of the methanol. Similar results are obtained with VBr_2. Methanolic solutions of VI_2 can be obtained by the precipitation reaction:

$$VCl_2 + 2KI = VI_2 + 2KCl\downarrow$$

Iodine compounds of quadrivalent vanadium can be prepared in the same way, specifically those of types $[VOL_5]I_2$, where L = DMF or DMSO, and $VOI(OCH_3) \cdot 3$ pyridine.

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Complexes of VCl_2 can be divided into two groups: 1. Compounds of type $VCl_2 \cdot 4L$, which are blue or violet and have temperature-independent magnetic moments of ~3.8 BM. 2. Compounds of type $VCl_2 \cdot 2L$, which are green and have magnetic moments lower than the spin-only values and strongly temperature-dependent. X-ray and reflection spectra of the hydrates show that group 1 compounds contain isolated octahedra, whereas in compounds of group 2 the octahedra are fourfold edge-connected $[VCl_{4/2}L_2]$. Solution spectra show that VCl_2 is completely dissociated in all solvents.

$TiCl_4$ can be reduced in methanol to the trivalent state. A solvate $TiCl_3 \cdot 4CH_3OH$ can be isolated from such solutions, and can also be made to exchange its methanol. Thus blue $TiCl_3 \cdot 3DMF$ and green $TiCl_3 \cdot 2DMF$ have been isolated. $TiCl_3$ exists in solution as a 1:1 electrolyte: $[TiCl_2(DMF)_4]^+Cl^-$.

WCl_6 is reduced to the quadrivalent, or further to the trivalent, state in dilute solution containing HCl. Chloro complexes $[N(CH_3)_4]_2WCl_6$ and $[N(CH_3)_4]_3W_2Cl_9$ can be isolated from the reduced solutions. On reduction of concentrated solutions a green, acid-insoluble precipitate was formed, of composition $W_2Cl_4(OCH_3)_4(CH_3OH)_2$; single-crystal photographs show a W—W distance of 2.47 Å and, at the present stage of the study, indicate union by oxygen bridges. A compound $[N(CH_3)_4]_2W(OCH_3)Cl_5$ can be isolated from the mother liquors. The monomeric compounds of W^{IV} have magnetic moments of ~1.6 BM, but the dimeric ones are almost diamagnetic with 0.26 BM.

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The Combustion of Elemental Boron in Air; A Thermodynamic Study[1]

By *Eberhard Büchner* and *Ingo Husmann*[*]

Boron is used as an additive for improving the performance of rocket propellants; however, it does not suffice to energize a propulsive unit having only one thrust chamber. Satisfactory results have been obtained only with an experimental set-up having two thrust chambers[2] in which the boron is heated in the first chamber and then burnt in the second in the presence of air.

On combustion of boron in air a predominantly gaseous, homogeneous or heterogeneous mixture is formed whose composition can be determined by a newly derived method of calculation. In the case of heterogeneous mixtures the separation of boric anhydride as condensed phase is taken into consideration. Elemental (unchanged) boron occurs as condensed phase in mixtures containing little oxygen. Further calculations were carried out for the case of boron nitride being present as condensed phase.

The above mentioned method of calculation takes into consideration the possible formation of the following species during combustion of boron in air: B, B_2O_3, B_2O_2, BO_2, BO, BN, N_2, N, NO, O_2, and O. If sufficient air is supplied to the system, considerable amounts of BO_2 are formed in addition to the main product of combustion B_2O_3.

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In an heterogeneous system with liquid B_2O_3 the accompanying gaseous phase is, in accord with the supposition of the method of calculation (sliding equilibrium), in equilibrium with gaseous boron oxides, so that the proportion of liquid B_2O_3 can be calculated by difference.

If the total composition is known then the enthalpies of the combustion products at given temperatures and pressures are also known, and an enthalpy-entropy curve can be plotted after calculation of the respective entropy values. The thrust chamber isobars each intersect the isenthalpic lines of the calorific value of the mixture at a point from which the isentropically assumed expansion occurs.

The intersection of these isentropic lines with the expansion isobar (*e.g.* 1 bar under ambient conditions) afford the enthalpy difference which is convertable into kinetic energy and from which the emission velocity of combustion products after having passed the nozzle of the second thrust chamber can be calculated. For a mixture of boron + air, $\lambda = 1.1$[3], the discharge rate for an expansion ratio 20:1 is 1893 m/s, the thrust chamber temperature under a pressure of 20 bar is 2717 °K, and the expansion temperature (20:1) 2070 °K.

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Organic Reactions in the Plasma of Glow Discharges

By *Harald Suhr*[*]

When electrons with an energy of a few eV impinge on organic molecules, the latter are partially altered and rearrangements, fragmentations, or, at high pressures, bimolecular processes can occur. Some of these processes have long been known but were not suitable for preparative purposes because in previous work the substances were largely destroyed with formation of low-molecular gases and tar. A procedure has now been worked out by which electron impact processes can be utilized preparatively. The apparatus is similar to that for vacuum distillation in which a high-voltage or high-frequency glow discharge is produced in the vapor space. Simple laboratory apparatus (with about 100 watts) produce 0.1–1 mole of product per kWh.

A number of reactions occur particularly well in the plasma. They were worked out first with the parent compounds, but can be extended to substituted compounds. High yields are obtained in dehydrogenating dimerization, *e.g.*, of benzene to biphenyl and of methylated aromatic compounds to 1,2-diarylethanes. Rearrangement of alkyl aryl ethers and *N,N*-dialkylanilines to respectively, alkylphenols and *N*-alkyl derivatives of alkylated anilines, and *cis-trans*-isomerizations, are also among favored plasma reactions. Among eliminations, particularly good yields are obtained in decarbonylations, *e.g.*, of benzophenone to biphenyl, of camphor to trimethylbicyclohexane, and of naphthols to indenes, and in decarboxylations of carboxylic acids and their anhydrides to hydrocarbons. Dehydrogenations with ring closure, *e.g.*, the reaction of diphenylamine to give carbazole, and of hydroxybiphenyl to give dibenzofuran illustrate interesting possible applications of plasma chemistry.

Plasma reactions take place mainly through radicals. The electrons transfer the energy of the external field to the molecules. This yields excited molecules, ionized molecules, or negative ions, which give the products either directly or after decomposition to radicals. Different mechanisms are found with individual classes of compound; some resemble those of pyrolysis, others those of photolysis or the processes in the mass spectrometer, and yet others have no relation to known mechanisms.

The reactions of organic molecules in the plasma offer interesting preparative possibilites. Several processes have been worked out on a laboratory scale; application on an industrial scale is certainly a possibility.

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New Sulfides of Metals

By *Welf Bronger*[*]

If the binary metal sulfides are considered in relation to their positions in the Periodic Table it is noticeable that very marked changes in properties occur near where the transition metals are inserted. The structure shows this particularly clearly: thus sulfides crystallize in salt-like structural types when derived from metals that have empty or completely filled d shells—to a smaller extent this is true also for metals with half-occupation—whereas sulfides of metals with partially filled d shells crystallize in structural arrangements where metal-metal interaction can be recognized. In this connection it appeared interesting to synthesize and study the structure of sulfides that contain both a main-group metal and a transition metal in ternary compounds.

Sulfides with heavy alkali metals on the one hand and with d elements on the other, were prepared by reactions in a melt under an inert gas. The starting materials were mixtures of alkali-metal carbonates or sulfides, transition metal, and sulfur. The following phases were thus synthesized:

$K_2Mn_3S_4$	$KFeS_2$		$K_2Ni_3S_4$
$Rb_2Mn_3S_4$	$RbFeS_2$	$Rb_2Co_3S_4$	$Rb_2Ni_3S_4$
$Cs_2Mn_3S_4$	$CsFeS_2$	$Cs_2Co_3S_4$	$Cs_2Ni_3S_4$
			$K_2Pd_3S_4$
			$Rb_2Pd_3S_4$
			$Cs_2Pd_3S_4$
			K_2PtS_2

X-ray investigation of single crystals showed that the ferrates have a structure characterized by edge-junction of the sulfur tetrahedra surrounding the iron atoms[1, 2] to form chains. In the manganates and cobaltates these sulfur polyhedra were joined by edges two-dimensionally into layers[3, 4]. In the palladates[5] and platinate[6] (the structure of the nickelate is still unknown) the ligands surround the transition metal in a planar arrangement, and the sulfur rectangles are joined by sides to give here too either layers or chains. In general, the structures of these compounds

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permit differentiation into sulfides with a greater similarity to alloys and the more salt-like complex compounds of the transition metals. The more metallic structural units are distinctly separated from the ionic ones by formation of layers or chains.

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Problems of High Speed Liquid Chromatography

By *Heinz Engelhardt*[*]

The theoretical relations derived for gas chromatography are valid also for liquid chromatography. However, the differences in the relative numerical values of the physical quantities (viscosity, diffusion coefficient, *etc.*) concerned in, for instance, the equation for zone spreading as a function of flowrate cause a shift in the relative influences of the various terms of this equation.

Thus the longitudinal diffusion term (the B term) has very little influence in liquid chromatography, since the rate of diffusion in the mobile phase is slower than in gases by a factor of 10^4. On the other hand, this same slow diffusion leads to preponderance of the term (the C_m term) for resistance to mass transfer in the mobile phase, namely that between the moving mobile phase between the particles and the stagnant mobile phase in the pores of the carrier. This band broadening can be overcome to some extent by decreasing the depth of the pores; this can be effected by decreasing the diameter of the particles ($<10\,\mu m$), since then the pore depth also becomes smaller, or by using thin-layer particles (porous layer beads) in which a thin porous surface layer ($\sim 1\,\mu m$) is placed on an inpenetrable core. This surface layer can be produced either by etching the surface of the particles, as in the carrier material Corning GLC 100 (Corning Glass Works, Corning, N. Y.) or by precipitating a thin porous layer of silica gel as in the carrier materials Corasil (Waters Assoc., Framingham, Mass.) and Zipax (Dupont, Wilmington, Del.). If the particle diameter is increased, then, in order to obtain the same flowrate, a higher pressure must be applied, the limits being set by the apparatus. Such particles were compared by observing the band broadening in relation to velocity (H. vs. velocity) and the number of effective plates/sec (measure of the speed of analysis).

The carriers differ in their loading capacity for the stationary phase. Surface-etched particles give sticky fillings even with light loading (0.4% of 3,3'-oxydipropionitrile), whereas the others can be much more heavily loaded (up to 2.6% of 3,3'-oxydipropionitrile) without appearing sticky. The number of effective plates/sec created is largest with Zipax. If, however, the difference in particle size is taken into account, Corasil and Zipax appear to be equal as regards the possible speed of analysis at equal pressure drop. Comparable values were obtained for the Corning glass beads only with substances that were very strongly retarded on the other carriers.

Corasil and Zipax are active adsorbents because a silica gel with a large specific surface area is used for the porous surface layer. This activity is evidenced in a variety of ways: The relative retention is a function of the amount of stationary phase on the support. The uncoated carrier adsorbs stationary phase from the solvent saturated with the stationary phase until a steady state is reached. Reproducible results cannot be obtained with loadings lower than that corresponding to this steady state. Only with the Corning glass beads are the values of relative retention independent of the amount of loading.

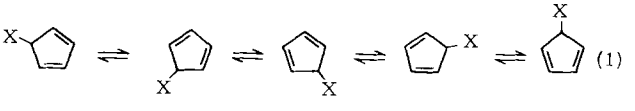
If all of the pores on a porous carrier are almost completely filled with stationary phase (*e.g.*, Porasil A with 100% w/w of 3,3'-oxydipropionitrile), band broadening in the stationary phase preponderates and lower plate heights are found for strongly retarded substances than for those eluted at the beginning. With these heavily loaded columns there is no reasonable loss of stationary liquid phase (using completely saturated eluants) due to mechanical erosion which limits the life of columns with porous layer beads. On these columns the sample size can be very large without overloading.

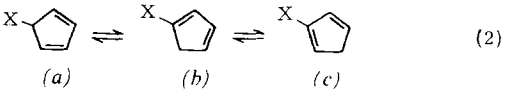
Lecture at Erlangen on January 22, 1971 [VB 285 IE]
German version: Angew. Chem. *83*, 411 (1971)

Cyclopentadienylboranes

By *Hans Grundke* and *P. I. Paetzold* (lecturer)[*]

σ-Cyclopentadienyl compounds XCp are subject to, *inter alia*, two types of equilibration, namely, valence tautomerism (1) and sigmatropic hydrogen shift (2):





When $X = R_2Al$ only reaction (1) is observed, when $X = R_3Si$ both reactions occur, but when $X = R_3C$ only reaction (3) takes place. How do cyclopentadienylboranes R_2BCp behave?

We prepared cyclopentadienyldiethylborane Et_2BCp *(1)* [and analogously diethyl(methylcyclopentadienyl)borane *(2)*] by reaction of chlorodiethylborane-pyridine with NaCp and subsequent removal of the pyridine by BF_3:

$$Et_2BCl\cdot Py \xrightarrow[-NaCl]{+NaCp} Et_2BCp\cdot Py \xrightarrow[-BF_3\cdot Py,\ -OEt_2]{+BF_3\ OEt_2} \underset{(1)}{Et_2BCp}$$

The by-way through the pyridine adduct is necessary since, in the presence of Lewis acids such as free Et_2BCl, *(1)* rapidly dimerizes by a Diels-Alder reaction; this dimeriza-

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tion occurs slowly at room temperature, but in one minute at 75 °C even in absence of a catalyst.

The ^{1}H-NMR spectrum of *(1)* contains signals with the following shifts from TMS (relative intensities in parentheses): $\tau = 0.7$ to -1.6 (10), -3.17 (2), -6.79 (2), and -7.50 (1); on general experience these signals can be ascribed to the two ethyl groups, a CH_2 group, and two olefinic CH groups. Reaction (1) is excluded by the CH_2 signal, and similarly isomer *(a)* in equilibrium (2) can be excluded. *(c)* is excluded because it is known that with boron the nuclear resonance frequency of *ortho*-ligands is lowered (*e.g.*, with compounds $C_6H_5BX_2$ and $C_6F_5BX_2$), so that the spectrum shows the existence of only one *ortho*-olefinic proton, as in *(b)*. Moreover, a CNDO-MO calculation[1] shows *(b)* to be about 7 kcal more stable than *(c)*.

The fission of the signals of two olefinic protons in the ratio 1:1 in the spectrum of *(2)* then accords with expectation.

The ^{1}H-NMR spectrum of the dimers of *(1)* contains signals for only two olefinic protons, at -6.35 and -6.55 ppm, together with signals of 28 other protons at higher shifts; hence follows that the two bulky boryl groups are bound to olefinic centers and, as expected, not to the junction centers of the cycloaddition. However, the diene components then cannot have structure *(b)* but must be *(c)*—an indication that there is an equilibrium between *(b)* and *(c)* in which the more stable *(b)* preponderates greatly.

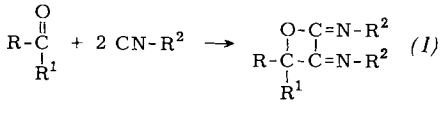
Lecture at Aachen on January 22, 1971 [VB 287 IE]
German version: Angew. Chem. *83*, 447 (1971)

[1] We thank Dr. *J. Fleischhauer*, Aachen, for the MO data.

New Synthesis of Heterocycles by means of Isocyanides

By *H.-J. Kabbe*[*]

Numerous aliphatic aldehydes and ketones, as well as aromatic aldehydes, react with isocyanides in the presence of catalytic amounts of boron trifluoride, to give 2,3-bis(alkylimino)oxetanes *(1)*[1]:

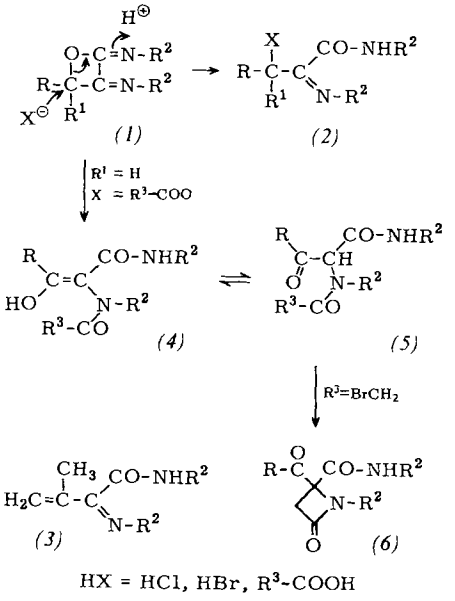


(1)

These oxetanes are remarkably stable both thermally and towards bases but can be cleaved by acids HX. This normally affords the β-addition products *(2)*, but occasionally unsaturated amides such as *(3)* are formed by isomerization[2].

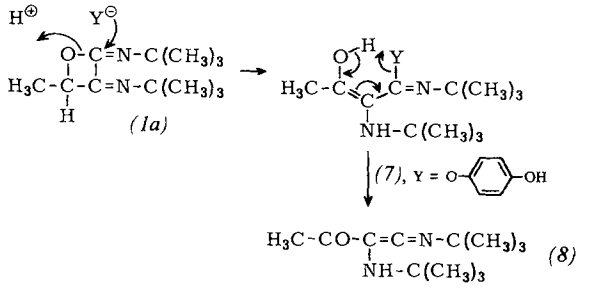
When the oxetanes *(1a)* are derived from aldehydes their reaction with carboxylic acids leads to acyl migration and formation of α-(acylamino)-β-hydroxyacrylamides *(4)*; if bromoacetic acid is used as addend, hydrogen bromide is split off from the tautomeric keto form *(5)* and the β-lactam *(6)* is obtained[3].

Neutral, weakly acidic, or basic compounds HY add to *(1a)* only under the influence of an additional acid and



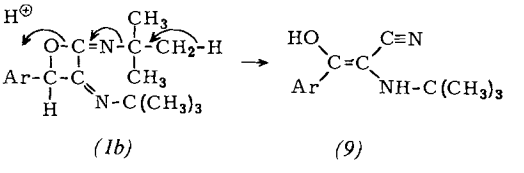
HX = HCl, HBr, R^3-COOH

then to the acyl-carbon, yielding compounds such as *(7)* (with hydroquinone/boron trifluoride). *(7)* easily splits off hydroquinone, giving the ketene imine *(8)*[4].



(8)

In the presence of approximately equimolar amounts of boron trifluoride, oxetanes *(1b)* prepared from aromatic aldehydes and *tert*-butyl isocyanide split off isobutene and pass into the cinnamonitriles *(9)*.



(1b) *(9)*

Lecture at Tübingen on January 29, 1971 [VB 288 IE]
German version: Angew. Chem. *83*, 448 (1971)

[1] *H.-J. Kabbe*, Chem. Ber. *102*, 1404 (1969).
[2] *H.-J. Kabbe*, Chem. Ber. *102*, 1410 (1969).
[3] *H.-J. Kabbe* and *N. Joop*, Liebigs Ann. Chem. *730*, 151 (1969).
[4] *H.-J. Kabbe*, Chem. Ber. in the press.

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Rheological and Boundary Layer Problems in Printing

By *W. Kunz*[*]

All printing processes involve the transference of printing ink onto substrate and, at least in the classical processes—letterpress, offset, and gravure printing—interaction takes

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place between liquids (printing inks) and solids (material to be printed on). These interactions are determined by the rheological properties of the liquids and by boundary-layer physical factors.

These interactions between different materials appear most decisive in the gravure process, in which a very low-viscosity printing ink is transferred from very small hollows that are etched to different depths. A problem arising in this process concerns the transference: the rate of transference is in the order of 2 milliseconds whereas all viscosity measurements—whether carried out with a rotation viscometer or with a cup viscometer—require seconds to minutes.

Two instruments have been developed for determining boundary-layer physical factors such as surface tension and contact angle *viz.* (i) an apparatus based on the bubble pressure method has been developed for the measurement of surface tension of the gravure inks, and (ii) a contact angle projector.

Curves which can be plotted for the wetting of printing material, and printing metals, with printing inks facilitate an interpretation of the failures in the printing process. With the aid of a special interference method, the behavior of the printing ink in a single etched hollow can be shown on a film[1]. Examination of the film showed that an exact impression of an individual hollow cannot be expected at the currently employed rates of printing with printing inks having the same rheological properties as those previously used in the profession.

Lecture at Darmstadt on February 5, 1971 [VB 289 IE]
German version: Angew. Chem. *83*, 448 (1971)

[1] Photographed by the Institut für Fotoanalyse Fritz Brill, Hofgeismar.

Relations between the Structural Elements and the Flow Behavior of Polymers and their Solutions

By *Martin Hoffmann*[*]

For viscosities η at low and high shear forces τ, critical shear forces τ_w of the structural viscosity, Young's moduli in the rubbery region of the relaxation behavior of entangled polymers, concentrations φ^+, above which entanglements form a network, and intrinsic viscosities $[\eta]$ one may formulate quantitative relations to structural parameters (molecular-weights M and their distribution, concentration, chemical nature, especially the molar volume V_g of the structural unit) or at least qualitative ones (different types of branching, distribution of chemical composition, sequences of like structural units, heterogenity as a consequence of phase separation, crystallinity). For $M < M_c$ viscosity at high temperatures is proportional to $M^{1.45}/V_g^3$. This applies also to $\eta_{\tau=\infty}$ for $M > 2\,M_c$, whilst $\eta_{\tau=0}$ is proportional to $M^{3.45}/V_g^7$. τ_w is proportional to φ^2/V_g^2.

These relations and their dependence on concentration are connected by the molecular weight M_c between entanglements, M_c being proportional to V_g^2/φ. In mixtures of chemically similar molecules having the same free volume and the molecular weights M_1 and M_2 an average M_v should be used in the above relations instead of φ_2 and M_2. The exponent a in M_v has a value of 0.72 for $M_v < 2\,M_c$ and a value of 0.87 for $M > 2\,M_c$. This leads directly to the concentration dependence of viscosity of such mixtures. $[\eta]$ is proportional to $(M_2/M_1)^{0.59} - 1$, which means that the end-to-end distance h is $h \sim M^{0.59}$ in contrast to assumptions used hitherto.

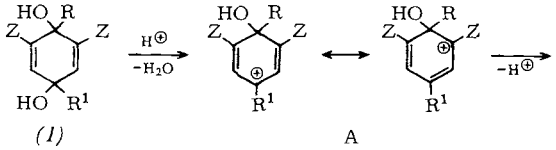
Lecture at Darmstadt on February 11, 1971 [VB 290 IE]
German version: Angew. Chem. *83*, 449 (1971)

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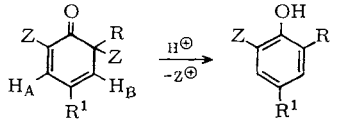
A New Route to the Oxepin System

By *Anton Rieker*[*]

In the presence of acid, cyclohexadienediols of type *(1)* (R = CH_3, C_6H_5, *p*-tolyl, *m*-tolyl, *p*-$(CH_3)_2NC_6H_4$; R^1 = C_6H_5, *tert*-butyl, mesityl, *p*-$CH_3OC_6H_4$; Z = CH_3, C_6H_5, *tert*-butyl) split off water, and the group R of the mesomeric cation (A) migrates to afford the 2-R-substituted cyclohexadienones *(2)*.



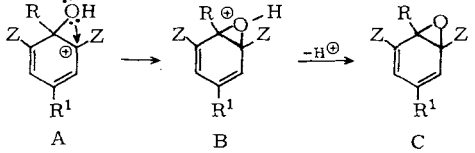
(1) A



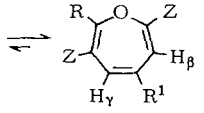
(2) *(3)*

When limited amounts of trifluoroacetic acid in methanol and low temperatures are used, then provided that Z = $C(CH_3)_3$, the compounds *(2)* can be isolated in substance [NMR spectra, AB system of the protons H_A/H_B with characteristic coupling (2.5 Hz); IR, intense carbonyl bands at 1650—1670 cm^{-1}; UV, λ_{max} = 305 to 330 nm, ε = 2500 to 7000, with usually a pronounced shoulder around 380 nm (n—π^* transtition of the C=O group)]. Using an excess of acid leads to fragmentation of the dienones *(2)* in which Z = *tert*-butyl, which affords the phenols *(3)* in yields exceeding 90% together with isobutene.

If R and Z are chosen so that the dienones *(2)* are sterically hindered (R = substituted phenyl; Z = *tert*-butyl) and the nucleophilicity and thus the migration aptitude of the group R is reduced below that of $(CH_3)_2NC_6H_4$ (namely, R = C_6H_5, *p*-tolyl, or *m*-tolyl, and R^1 is as above), then it



A B C



X = *(4)*

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could be shown by NMR spectroscopy that acidic rearrangement of the diols *(1)* gave a new intermediate X, which on further treatment with acid was converted into *(2)* and finally into *(3)*. When the experimental conditions were chosen suitably, the compounds X could also be isolated in crystalline form [for $R=p\text{-}CH_3C_6H_4$, $R^1=p\text{-}CH_3OC_6H_4$, $Z=C(CH_3)_3$ in CH_3OH at $-50°C$ with 1 equiv. of CF_3COOH in 70% yield; m. p. 115 °C].

NMR spectra (coupling of the β,γ protons: 0.7—1 Hz), IR spectra (C=C vibration at *ca.* 1635, ether bands at 1080 cm^{-1}), and UV spectra ($\lambda_{max}=310$—330 nm, $\varepsilon=3300$—8000) confirm the oxepin structure *(4)* of X. Further structural proof is provided by the ^{13}C Fourier transform NMR spectra. Photolysis of the oxepins *(4)* leads to 2-oxabicyclo[3.2.0]hepta-3,6-dienes. The oxepins must have been formed by 1,2-migration of the hydroxyl group of (A) to give (B) and deprotonation of (B) to the benzene epoxide (C).

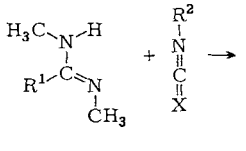
Lecture at Tübingen on February 12, 1971 [VB 291 IE]
German version: Angew. Chem. *83*, 449 (1971)

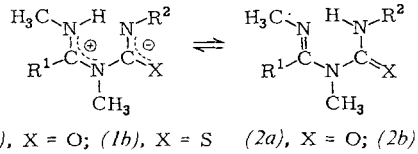
Hydrogen Bridges with Nitrogen as Donor and Acceptor

By *Gerhard Schwenker*[*]

The products obtained on reaction of amidines with heterocumulenes (isocyanates or isothiocyanates) differ according to the type of substitution of the amidine, the reactivity of the heterocumulene, and the experimental conditions[1]. Amidines with hydrogen on N-1 give dipolar molecules *(1)* which afford carbamoyl- *(2a)* or (thiocarbamoyl)-amidines *(2b)* by proton transfer.

In *(2a)*, but not in *(2b)*, there are strong intramolecular hydrogen bridges recognizable by the bathochromic shift of the NH bands to around or below 3000 cm^{-1}. The cause is as follows: In an unperturbed system of five sp^2-hybridized atoms the donor and the acceptor approach one another to within about 2.4 Å in the conformers able to form intramolecular hydrogen bridges. This requires an extremely strong, symmetrical bridge, which however is unlikely. Thus one must assume appreciable widening of the relevant angle and as a consequence a closer approach of the peripheral substituents. The range of existence of these conformers is thus limited by the steric demands of the peripheral substituents and size of the angle broadening required, the latter decreasing with increasing polarity of the N—H bond and thus with increasing bond enthalpy. In *(2b)* the sulfur atom, which is larger than the oxygen atom, causes such great steric hindrance that one of the other conformers is thermodynamically more favorable.





(1a), X = O; *(1b)*, X = S *(2a)*, X = O; *(2b)*, X = S

Experimental findings support this view. Systematic increase in size of the substituents R^1 in *(2a)* (H, CH_3, C_2H_5) first increases the bathochromic shift of the NH bands, this being explained by the compression of the bridge; with iso-C_3H_7 and *tert*-C_4H_9, however, there is no longer any indication of hydrogen bridges, so that for *(2a)* with substituents of this size a conversion into another conformation is assumed. Increasingly strongly electron-attracting substituents R^2 (CH_3, C_6H_5, *p*-C_6H_4Cl, *p*-$C_6H_4NO_2$) permit closer approach of the donor and acceptor owing to increase in the N—H bond moment; this can be recognized by increasing bathochromic shifts of the NH bands. In the sulfur compounds *(2b)*, however, even C_6H_5 as R^2 leads to such an increase in the acidity of the N—H bond that the proton transfer *(1)*→*(2)* no longer occurs, and exchange reactions take place instead.

Lecture at Hamburg (Germany) on February 16, 1971 [VB 292 IE]
German version: Angew. Chem. *83*, 449 (1971)

[1] *G. Schwenker* and *R. Kolb*, Tetrahedron, *25*, 5437, 5549 (1969).

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Improved Determinations of Intermolecular Potentials

By *Bernhard Schramm*[*]

A knowledge of intermolecular potentials is an essential basis for statistical calculations of macroscopic properties of matter. Information about potential energy curves can be gained, *e.g.* from the temperature dependence of the virial coefficients or transport phenomena of gases and from measurements of the scattering cross-section with the aid of molecular beams.

Let us assume that the potential energy between two particles depends only on their mutual separation. It must be made up of a long-range attractive component (responsible for condensation of gases) and a repulsive component that is effective at shorter ranges (responsible for separation in crystal lattices). Superposition of the two components gives a potential energy minimum having coordinates r_{min} and ε. The best known expression for potential energy that contains only these two free parameters is the Lennard-Jones potential:

$$\varphi(r)=\varepsilon[(r_{min}/r)^{12}-2(r_{min}/r)^6]$$

On suitable choice of r_{min} and ε, it can be used for calculation of the second virial coefficient and transport parameters over wide ranges of temperature. However, more accurate measurements uncover deviations that cannot be accounted for by experimental error. Moreover, two different sets of potential parameters are required for calculations of virial coefficients and transport factors respectively.

These drawbacks can be lessened by permitting free choice of a third parameter such as the power of the repulsive term. This leads to the $n-6$ potentials by way of the equation:

$$\varphi(r)=\varepsilon/n-6[6(r_{min}/r)^n-n(r_{min}/r)^6]$$

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An increase in n makes the potential curve steeper and the potential trough thus narrower. Nevertheless, this modification of the potential curve does not suffice to accurately and simultaneously reproduce the virial coefficients and the viscosity in a large temperature range. For such a satisfactory representation it is necessary to be able to vary the long-range attractive forces and the repulsive forces independently of each other.

Table. Potential parameters and potential for argon.

Potential parameters r_{min} (Å)	ε/k[a] (°K)	Potential
3.84	119	Lennard-Jones 12-6 potential
3.77	148	11-6/24-6 potential
3.67	153	*Klein* and *Hanley*, 11-6-8 potential [1]
3.757	147.7	*Barker* and *Pompe* [2]
3.81	138	*Dymond* and *Alder* [3]

[a] k = Boltzmann's constant.

This condition is fulfilled if the intermolecular potential for distances $r \leqq r_{min}$ (to the left of the potential minimum) is described by a different $n-6$ potential from that used for $r \geqq r_{min}$. In this way the available data for the virial coefficients and the viscosity of argon can be reproduced within the limits of experimental accuracy by an 11-6/24-6 potential (*i.e.* $\varphi(r)$ = 11-6 potential for $r \leqq r_{min}$, $\varphi(r)$ = 24-6 potential for $r \geqq r_{min}$). In the Table the potential parameters found are compared with those considered for argon by other authors within the past few years. It clearly appears that the intermolecular potential of argon has a deeper trough and a steeper course of the attractive portion than the 12-6 potential. Molecular beam measurements afford $r_{min} = 3.7 \pm 0.2$ Å and $\varepsilon/k = 147 \pm 3$ °K[4].

Lecture at Heidelberg on January 12, 1971 [VB 293 IE]
German version: Angew. Chem. *83*, 450 (1971)

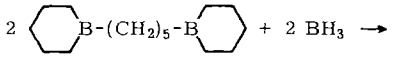
[1] *M. Klein* and *H. J. M. Hanley*, J. Chem. Phys. *53*, 4722 (1970).
[2] *J. A. Barker* and *A. Pompe*, Austral. J. Chem. *21*, 1683 (1968).
[3] *J. H. Dymond* and *B. J. Alder*, J. Chem. Phys. *51*, 309 (1969).
[4] *M. Cavallini, G. Gallinaro, L. Meneghetti, G. Scoles*, and *U. Valbusa*, Chem. Phys. Lett. *7*, 303 (1970).

SELECTED ABSTRACTS

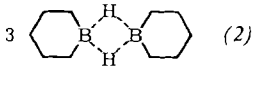
One-step preparation of nitriles from carboxylic acids is possible by a new method described by *J. Lücke* and *R. E. Winkler*. The acid (1 mole) is heated for one hour with amidosulfuric acid (1.5–2 mole) and urea (1–1.5 mole). Yields are good. For example, *o*-chlorobenzoic acid affords the nitrile in 85–90% yield; with urea alone the yield amounts to *ca.* 50%; with amidosulfuric acid alone it is about 7%. / Chimia *25*, 94 (1971) / –Ee.

[Rd 339 IE]

Bis(perhydroborin) *(2)* **and** ***B*-alkylperhydroborins** have been prepared by *H. C. Brown* and *E.-I. Negishi via* a simple new route. 1,5-Bis(perhydroborin-1-yl)pentane *(1)* reacts rapidly with borane at 25 °C to give bis(perhydroborin) *(2)*. The starting material *(1)* is obtained by hydroboration of



(1)



(2)

1,4-pentadiene with borane and subsequent thermal isomerization. *(2)* reacts with olefins at 25 °C to give *B*-alkylperhydroborins in excellent yield. If these compounds are required only as intermediates it is unnecessary to isolate the bis(perhydroborin) or the *B*-alkylperhydroborins. / J. Organometal. Chem. *26*, C67 (1971) / –Kr.

[Rd 340 IE]

Tetrakis(pentacarbonylmanganese)uranium, the first complex to have a bond between uranium and a transition metal, has been obtained by *R. L. Bennett, M. I. Bruce*, and *F. G. A. Stone*. Solutions of sodium pentacarbonylmanganate and uranium tetrachloride in THF, which had turned deep red on standing at room temperature for 3 h, afforded a 50% yield of an orange powder that proved to be pure $U[Mn(CO)_5]_4$. It is extremely sensitive to air and decomposes at 180 °C. / J. Organometal. Chem. *26*, 355 (1971) / –Ee.

[Rd 341 IE]

Use of ferrate(VI) ion as a new selective oxidizing agent is reported by *R. J. Audette, J. W. Quail*, and *P. J. Smith*. K_2FeO_4 rapidly oxidizes primary amines and alcohols to aldehydes and secondary alcohols to ketones at room temperature. Double and triple bonds, aldehyde groups, tertiary alcohol- and amine functions are not affected. The reaction must be carried out in an aqueous, strongly basic medium. Yields are moderate to good and no by-products are formed. Formation of aldehydes from primary amines is explained by hydrolysis of imine intermediates. / Tetrahedron Lett. *1971*, 279 / –Kr.

[Rd 342 IE]

Silylammonium compounds have been obtained by *R. E. Highsmith, J. R. Bergerud*, and *A. G. MacDiarmid*. Whereas treatment of silylamines with protonic acids usually leads to Si—N bond cleavage, reaction with $HCo(PF_3)_4$ and $HCo(CO)_4$ below 0 °C results in protonation of the amino group. $(CH_3)_2N—Si(CH_3)_3$ gave $[(CH_3)_2N(H)Si(CH_3)_3]^+ [Co(PF_3)_4]^-$ *(1)* and the tetracarbonylcobaltate *(2)* respectively. This compound could also be obtained from $(CH_3)_2NH$ and $(CH_3)_3SiCo(CO)_4$. Compound *(1)* sublimes at about 80 °C in vacuum. Compound *(2)* decomposes at room temperature to give darkly colored products. / Chem. Commun. *1971*, 48 / –Ee.

[Rd 346 IE]

Evidence for the existence of a "silylenoid" species in the *trans*-$PtCl_2[(C_6H_5)_3P]_2$-catalyzed disproportionation of

pentamethyldisilane *(1)* has been found by *K. Yamamoto, H. Okinoshima,* and *M. Kumada.* The "dimethylsilylene" formed by α-elimination inserts into Si—H bonds to give homologs of *(1)*.

$$(CH_3)_3Si{-}Si(CH_3)_2H \xrightarrow[\text{complex}]{Pt} \sum CH_3[Si(CH_3)_2]\,H \quad (n=1-6)$$
(1)

Further support for this concept comes from the reaction of *(1)* with tolan in the presence of the platinum complex

$$2\,(CH_3)_3Si{-}Si(CH_3)_2H + 2\,C_6H_5{-}C{\equiv}C{-}C_6H_5$$
(1)
$$\downarrow\ PtCl_2[(C_6H_5)_3P]_2$$
$$2\,(CH_3)_3SiH + \text{(2)}$$

(2): a 1,4-disila-2,5-cyclohexadiene bearing H_3C, CH_3, H_5C_6, C_6H_5 substituents on the two silicon atoms.

which yields the disilacyclohexadiene derivative *(2)*. / J. Organometal. Chem. *27*, C31 (1971) / –Kr.

[Rd 343 IE]

Incorporation of S_2 and Se_2 units into rhodium and iridium complexes has been accomplished by *A. P. Ginsburg* and *W.E. Lindsell.* Under the conditions mentioned the complexes *(1)* and *(2)* gave the new compounds *(3)–(5)*:

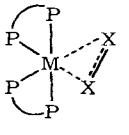
$$[Ir(dppe)_2]Cl + S_8 \xrightarrow[C_6H_6/CH_2Cl_2]{25\,^\circ C,\ 16\ h} [Ir(S_2)(dppe)_2]Cl$$
(1) *(3)*

$$[Ir(dppe)_2]Cl + Se_8 \xrightarrow[CH_2Cl_2]{20\,^\circ C,\ 72\ h} [Ir(Se_2)(dppe)_2]Cl$$
(1) *(4)*

$$[Rh(dmpe)_2]Cl + S_8 \xrightarrow[C_6H_6/THF]{25\,^\circ C,\ 16\ h} [Rh(S_2)(dmpe)_2]Cl$$
(2) *(5)*

$dppe = (C_6H_5)_2P{-}CH_2{-}CH_2{-}P(C_6H_5)_2$
$dmpe = (CH_3)_2P{-}CH_2{-}CH_2{-}P(CH_3)_2$

(3) and *(4)* are air-stable, *(5)* is hygroscopic. Structures having π-bonded S_2 and Se_2 units were deduced from the

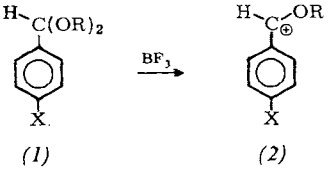


M = Rh, Ir
X = S, Se

NMR and IR spectra. Corresponding O_2 complexes are already known. / Chem. Commun. *1971*, 232 / –Ee.

[Rd 344 IE]

Stable arylalkoxycarbonium ions have been directly observed by *M. Rabinovitz* and *D. Bruck.* Treatment of acetals of type *(1)* with BF_3 in $CDCl_3$ at room temperature affords a stable, deeply colored, clear solution. The ionic nature of the dissolved product *(2)* was established by NMR spectroscopy. Charge delocalization plays an important role in stabilization of the carbonium ion. / Tetrahedron Lett. *1971*, 245 / –Kr.

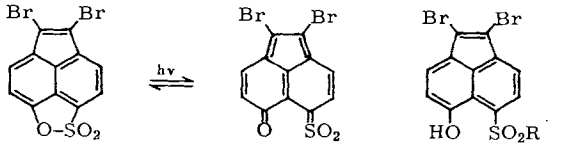


(1) *(2)*

R = CH_3, C_2H_5
X = H, CH_3, OCH_3

[Rd 345 IE]

5,6-Dibromoacenaphthyleno[5,5a,6-cd]-1,2-oxathiol 2,2-dioxide *(1)*, a precursor of the potential sulfene *(2)*, has been synthesized and studied by *S. T. Weintraub* and *B. F. Plummer.* Irradiation of *(1)* in anhydrous methanol (Hanovia 450-W lamp, Pyrex filter) at room temperature gave the sulfonic ester *(3)*. Compound *(3)* could also be



(1) *(2)* *(3)*, R = OCH_3; *(4)*, R = OH; *(5)*, R = –N⬠

prepared from *(1)* and CH_3O^-/CH_3OH. The acid *(4)* was obtained, after dissolution of the brown precipitate in water, from a methanol solution of *(1)* that had been kept in the dark for two weeks. Compound *(1)* reacts immediately with pyrrolidine (purple coloration) to give *(5)*. The authors interpret these and other findings in terms of the intermediacy of the sulfene *(2)*. / J. Org. Chem. *36*, 361 (1971) / –Ee.

[Rd 347 IE]

Esters of hypophosphorus acid, which were hitherto unknown, have now been prepared by two Russian research groups. *I. F. Lucenko, M. V. Proskurina,* and *A. A. Borisenko* obtained the alkyl esters *(1)* from the dialkoxychlorophosphanes and trialkylstannane in ether or tetrahydrofuran at 30 °C.

$$(RO)_2P{-}Cl + R_3SnH \longrightarrow (RO)_2PH \quad \text{(1)}$$

Esters with a small group R (methyl, ethyl) were not isolable; they decomposed to give yellow, polymeric solids. In contrast, esters having large R could be isolated by vacuum distillation. They are colorless liquids that fume in air while undergoing oxidation with considerable evolution of heat.—*M. G. Voronkov* and *L. Z. Martur* prepared trialkylsilyl esters of hypophosphorous acid by reaction of ammonium hypophosphite with dialkylaminotrialkylsilane or hexaalkyldisilazane at temperatures of

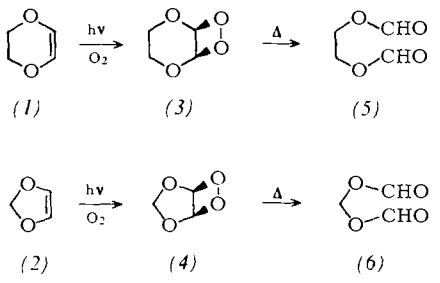
$$NH_4[PH_2O_2] + R_3Si{-}NR_2 \rightarrow HP(OSiR_3)_2 \quad \text{(2)}$$
$$NH_4[PH_2O_2] + R_3Si{-}NH{-}SiR_3 \rightarrow HP(OSiR_3)_2$$

about 100 °C. / Doklady Akad. Nauk SSSR *193*, 828 (1970); Zh. Obshch. Khim. *40*, 2135 (1970) / –Fa.

[Rd 348 IE]

Formation of stable bicyclic dioxetanes on addition of singlet oxygen to 2,3-dihydro-1,4-dioxin *(1)* and 1,3-dioxole *(2)* has been observed by *A. P. Schaap.* Compounds *(1)* and *(2)* are cleaved photooxidatively (at –78 °C in presence of a sensitizer) to give ethylene diformate *(5)* and methylene diformate *(6)* respectively. The

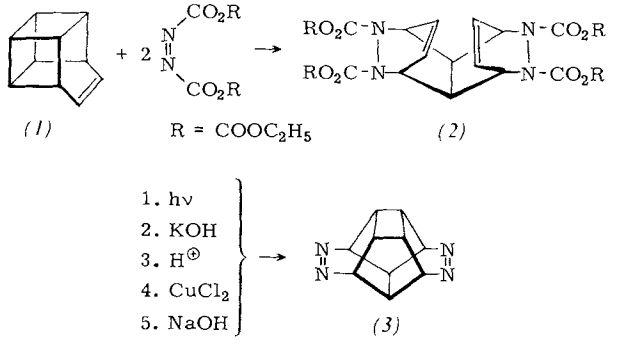
intermediacy of the bicyclic dioxetanes *(3)* and *(4)*, which are relatively stable at room temperature, was proved by NMR spectroscopy. Their thermal decomposition at 60 °C



leads quantitatively to *(5)* and *(6)*. Decomposition is accompanied by chemiluminescence in presence of a fluorescing hydrocarbon such as 9,10-dibromoanthracene. / 161st ACS Nat. Meeting, Abstracts of Papers, ORGN 109, 1971 / -Ma.

[Rd 349 IE]

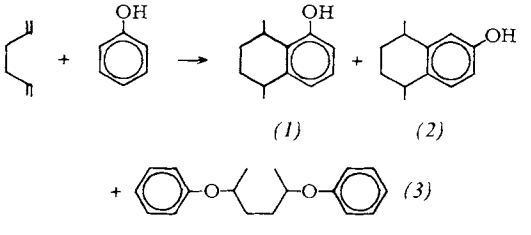
2,3,7,8-Tetraazahexacyclo[7.4.1.0^{4,12}.0^{5,14}.0^{6,11}.0^{10,13}]tetradeca-2,7-diene *(3)*, a potential pentaprismane precursor, has been synthesized by *Kei-wei Shen* and *L. J. Winters*. Compound *(3)* was obtained from pentacyclo-[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]dec-9-ene *(1)* and diethyl azodicarboxylate *via (2)* in a multi-step synthesis. It is thermally very stable, having a halflife of 18 h at 240 °C. Flash vacuum



pyrolysis gives 9,10-dihydrofulvalene as sole identifiable product. / 161st ACS Nat. Meeting, Abstract of Papers, ORGN 88, 1971 / -Ma.

[Rd 350 IE]

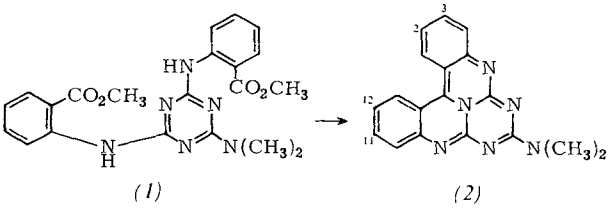
Cycloalkylation of phenol with 1,5-hexadiene in CS_2 (molar ratio 4:1) in presence of BF_3-ether is reported by *J. M. Balquist* and *E. M. Degginger* to produce 5,6,7,8-tetrahydro-5,8-dimethyl-1- and -2-naphthol *(1)* and *(2)* respectively, besides 2,5-diphenoxyhexane *(3)*. Reaction



involves initial formation of 5-phenoxy-1-hexene and 2-(1-methyl-4-pentenyl)phenol which react further to give *(1)* and *(3)* respectively. The *p*-alkylated major product *(2)* is formed by reaction of phenol with the diether *(3)*. / 161st ACS Nat. Meeting, Abstracts of Papers, ORGN 140, 1971 / -Ma.

[Rd 351 IE]

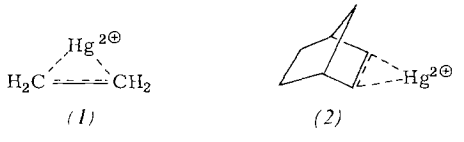
5,6,8,8b,9-Pentaazanaphth[3,2,1-*de*]anthracene *(2)*, a new ring system, has been obtained by *R. A. E. Winter* as product of a novel cyclization. Ring closure of the *s*-triazine derivative *(1)* in boiling acetic acid gave *(2)*, m.p. 302 °C, in 82% yield. Compound *(2)* has a conjugated 20 π-electron periphery and an additional lone pair on the central



nitrogen and may be regarded as the dibenzo analog of the [3,3,3]cyclazines. It is weakly basic, forms a monohydrochloride, and is dinitrated in the 2,12 or 3,11 positions. No deuterated product is formed in [D_4]acetic acid. / 161st ACS Nat. Meeting, Abstracts of Papers, ORGN 87, 1971 / -Ma.

[Rd 352 IE]

Stable mercurinium ions have been observed for the first time by *P. R. Clifford*. Treatment of 2-methoxyethylmercury chloride with $FSO_3H/SbF_5/SO_2$ solution at −78 °C was shown by NMR spectroscopy to yield the ethylenemercurinium ion *(1)* alongside protonated methanol. Similarly, *exo-cis*-3-hydroxy-2-norbornylmercury ac-



etate was found to give norbornylenemercurinium ion *(2)*. Propylene-, ethylethylene-, and cycloalkylene-mercurinium ions were also studied. / 161st ACS Nat. Meeting, Abstracts of Papers, ORGN 150, 1971 / -Ma.

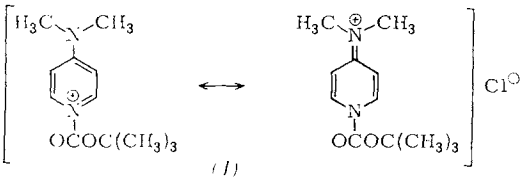
[Rd 353 IE]

S_3, thiozone, has been detected spectroscopically by *B. Meyer, T. Stroyer-Hansen, D. Jensen*, and *T. Oommen*. The species was found in molten sulfur at 300—700 °C, in red sulfur at 77 °K, in sulfur vapor at 450 °C/20 torr, and at 20 °K in noble gas matrices containing photolysis products of S_3Cl_2. All samples exhibited an absorption between 3600 and 4200 Å that can be assigned to thiozone, S_3. Sulfur vapor contains *ca.* 30%, liquid sulfur at 444 °C *ca.* 1%, the photolysis products of S_3Cl_2 in krypton at 20 °K *ca.* 90% of S_3. The species S_3 and S_4 are responsible for the red color of hot liquid sulfur. The presence of thiozone is the cause of the high reactivity of molten sulfur. / 161st ACS Nat. Meeting, Abstract of Papers, INOR 165, 1971 / -Ma.

[Rd 354 IE]

4-Dimethylamino-1-*tert*-butoxycarbonylpyridinium chloride *(1)* is suitable as a water-soluble reagent for *tert*-butoxycarbonylation of amines according to a report authored by

E. Guibé-Jampel and *M. Wakselman. (1)* is a stable compound that reacts with the Na salts of amino acids in aqueous solution. The reaction is very fast at 25 °C. The

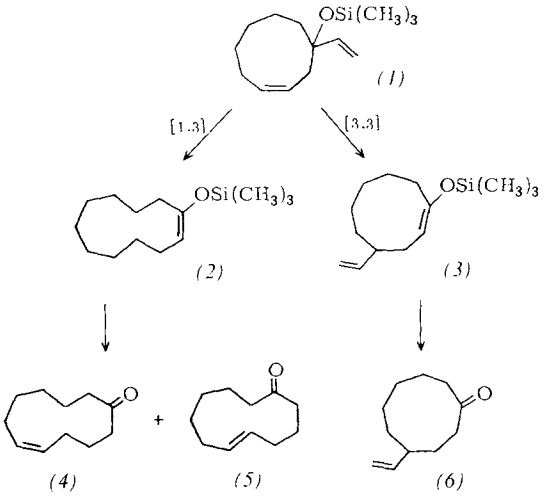


(1)

BOC amino acids can be isolated in good yields by solvent extraction. Examples: *N*-BOC-glycine, 85% yield; *N*-BOC-glutamic acid, 70%; N^{ε}-BOC-N^{α}-Z-L-lysine, 80% (Z = benzoxycarbonyl); *N*-BOC-serine, 60%; *N*-BOC-glycine ethyl ester, 90%. / Chem. Commun. *1971*, 267 / –Ma.

[Rd 355 IE]

Ring expansion by two C atoms on "siloxy Cope rearrangement" to give good yields of unsaturated cyclic ketones is described by *R. W. Thies*. For example, the trimethylsiloxy derivative of *cis*-1-vinylcyclonon-3-en-1-ol *(1)* undergoes thermal rearrangement *via* [1.3] and [3.3] sigmatropic



shifts to give six trimethylsiloxy enol ethers [four and two *cis-trans* isomers of *(2)* and of *(3)* respectively] whose hydrolyses lead to the ring-expanded ketones *(4)* and *(5)* and to the cyclononanone *(6)* in high yields. In contrast to the "oxy Cope rearrangement", the reaction is accompanied by neither significant polymer formation nor cleavage to the β-hydroxy olefin. The trimethylsiloxy derivatives are readily obtainable in good yields. / Chem. Commun. *1971*, 237 / –Ma.

[Rd 356 IE]

The vibrational spectra (IR and Raman) of oxalyl bromide in all physical states were recorded by *J. R. Durig, S. E. Hannum*, and *F. G. Baglin*. Whereas solid $(COBr)_2$ occurs only in the *trans* form, the spectra of the liquid contain bands that can be ascribed to the *cis* form. The free enthalpy difference between *cis* and *trans* forms amounts to 2.9 ± 0.1 kcal mol^{-1}, the *trans* form being the more stable of the two. At room temperature, $10 \pm 5\%$ of the liquid is in the *cis* form. Approximate values of the potential function parameters describing the rotation about the C—C bond are given. / J. Chem. Phys. *54*, 2367 (1971) / –Hz.

[Rd 357 IE]

Oxidation of thiacyclobutane and thiacyclopentane with oxygen initiated by Q-switched laser pulses was investigated by *F. P. Miknis* and *J. P. Biscar*. Varying amounts of oxygen were added to a constant amount of liquid C_3H_6S or C_4H_8S in a spherical Pyrex bulb and the gaseous mixture exposed to one pulse from a Q-switched ruby laser. Each pulse had a peak power of over 100 MW and a duration of about 20 ns. With oxygen partial pressures between 100 and 1500 torr the pulses initiated a reaction accompanied by emission of radiation in the entire gas volume. The major products were CO_2, SO_2, and H_2O, in addition H_2S, COS, CS_2, and C_2H_2 were found in amounts depending on the oxygen partial pressure. It is probable that the reaction is started by multiphoton absorption: without Q-switching, *i.e.* if the pulse energy is released over a time interval about 10^3 times longer, no reaction occurred. / J. Phys. Chem. *75*, 725 (1971) / –Hz.

[Rd 358 IE]

BOOK REVIEWS

Radical Ions. Edited by *E. T. Kaiser* and *L. Kevan*. Interscience Publishers, a Division of John Wiley and Sons, New York–London 1968. 1st Edit., ix, 800 pp., numerous figures, bound, £14.00.

With its 13 selected topics from the realm of the chemistry and physical chemistry of radical ions, all of them written by eminent experts, this book offers a near comprehensive survey of the most important modern aspects of the chemistry of cation- and anion-radicals. The single unifying theme—how could it be otherwise—is ESR spectroscopy and the relevant orbital theory. Thus, anyone interested in, for example, the radicals formed by γ-irradiation, does not need to read the previous eight chapters. The book begins with a survey of electron spin densities and their determination from the coupling constants observable in the ESR spectra. The following chapters, however, are all concerned with more specific topics from the chemistry of organic radicals: metal ketyls and related radical ions, semidione radical anions, radical cations, the effect of substituents on the electron spin densities in aryl radicals and its theoretical importance, aromatic anion radicals, radical anions in Group IV elements, and sulfur-containing aromatic radical anions. The book ends with the structure of inorganic radicals, fragments from the irradiation of solid ions, and the electron spin resonance of complex ions of transition metals of the first row.

Each chapter is clearly written in the manner of an essay review and is provided with a good selection of references and graphic illustrations. There are no extensive historical introductions, but emphasis is placed on modern developments. Since a great variety of topics are covered, the reader may treat the work selectively. It is, infact, more a collection of excellent individual articles, rather than a coherent entity. The thoroughness and conciseness with which the individual chapters are written provide an excellent opportunity for readers, even those not directly concerned with this field, to gain an idea of the broad outlines of the rapidly developing radical chemistry. The book is indispensable for the library of any institute of chemistry or physical chemistry.

Karl Dimroth [NB 942 IE]

Phase Equilibria, Basic Principles, Applications, Experimental Techniques. By *A. Reisman*. Academic Press, New York–London 1970. xi, 541 pp., bound $27.50.

Until the mid-1950s, interest in phase equilibria was almost exclusive to metallurgists. Nowadays it calls to mind topics such as semiconductors, nuclear technology, space technology, zone melting, chemical transport reactions, and crystal growing. Whereas the metallurgist was mainly concerned with equilibria of condensed phases at normal pressure, both the gas phase and the influence of high pressures are nowadays becoming increasingly important.

This was one reason why the author wrote the present book. Another reason was that the existing books dealing with this topic use a phenomenological approach and mainly graphical representation at the expense of a more detailed mathematical treatment. New paths in this connection have been opened up by computers.

The thermodynamic basis is first elaborated and tested on the equilibria of one-component systems. In the subsequent binary and pseudobinary systems, the author considers only ideal model systems and deliberately omits such concepts as fugacity or activity. A systematic mathematical treatment of these ideal systems provides an understanding of the laws to which the observed types of phase equilibria are subject. In particular, numerous examples are given to show quantitatively the influence of parameters such as the melting points and heats of fusion of the pure components, dissociation or association in melts or solids, external pressure, and the vapor pressures of the components. The calculated model systems, for which graphs are constructed, are compared with examples from the literature. Even systems as unusual as those that exhibit continuous solid solution formation with a melting minimum are calculated on this basis. A few chapters dealing with ternary systems are then included. The picture is rounded off by examples of applications, such as purification by distillation or zone melting and chemical transport reactions.

The last, less successful, chapter deals with experimental methods. This discussion totally ignores some important methods, such as EMF or calorimetric measurements. Other aspects, such as the operation of a thermocouple, are discussed in too much detail.

In general, the book should facilitate the approach to the complex field of phase equilibria, and a great help here is the fact that it has been restricted to model systems. It is thus suitable both for the advanced student and for the practical worker who wish to forge ahead to the fundamental rules of phase equilibria.

Hans Rau [NB 947 IE]

The Theory of Adsorption and Catalysis. Physical Chemistry, A Series of Monographs. By *A. Clark*. Academic Press, New York – London 1970. 1st ed., x, 418 pp., bound DM 19.50.

The book presents a survey of the present position in the theoretical treatment of adsorption and catalysis. It is in the nature of things that theories based on models occupy the foreground in the first part, which is devoted to adsorption, whereas empirical relations receive more attention in the second part, which deals with catalysis.

A brief outline of the thermodynamics of adsorption serves as an introduction. This is followed by the discussion of localized and non-localized adsorption on homogeneous and heterogeneous surfaces for systems without interaction between neighboring particles and for systems with such an interaction. Adsorption isotherms, heats of adsorption, entropies of adsorption, *etc.*, are derived for these various adsorption systems with the aid of statistical thermodynamics.

One chapter each is devoted to the adsorption forces in physisorption, in chemisorption on metals, and in chemisorption on semiconductors. The dispersion and repulsion forces are discussed, as well as the analogy between chemisorption bonding and chemical bonding and the models for a quantum-mechanical treatment of chemisorption. The description of chemisorption on semiconductors is based mainly on the Hauffe and the Wolkenstein views. The first part of the book ends with a chapter on the kinetics of chemisorption.

The second part is introduced by an examination of the relation between adsorption and catalysis. The kinetics of heterogeneous catalytic reactions is considered separately for reactions in which diffusion plays no part and for diffusion-controlled reactions.

The "geometric factor" is discussed at length in connection with the effects of lattice structure, defects, and particle size on catalytic activity. The "electronic factor" is discussed for metals and semiconductors. A final chapter deals with the adsorbed species and their role in heterogeneous catalysis.

The extensive bibliographies cite references up to 1969.

This well-written summary of present-day knowledge will be a welcome aid to anyone who is concerned with the fundamentals of adsorption and catalysis.

Gerd Wedler [NB 951 IE]

Computer Programs for Chemistry. By *D. F. Detar*. W. A. Benjamin Inc., New York 1968. 1st ed., xx, 207 pp., bound $14.75.

The evaluation of experimental results or the calculation of molecular properties with the aid of computer programs is becoming increasingly important in chemistry. Whenever the considerations are based on a complicated calculation, it is advisable to use programs devised by personnel

who have familiarized themselves with programming problems.

The purpose of "Computer Programs for Chemistry" is to provide readymade programs that can be used directly for the solution of certain chemical problems or that can be incorporated into other programs after slight modification. The present first volume contains FORTRAN IV programs by several authors from the fields of NMR spectroscopy and kinetics, as well as a program for plotting curves (PLOTLN). LAOCN3 and the programs NMRIT and NMREN calculate the position and the intensity of the NMR lines from assumed chemical shifts and coupling constants. If the calculated spectrum is similar to the experimental spectrum, the input parameters can be improved by an iteration process. LSG or LSKIN 1 evaluates the data for a first order reaction, and calculates the best value for the rate constant and the initial and final values of the variables.

All the programs were reproduced by photomechanical reduction from the original programs, and the input and output for one example is given for each program. In addition to the explanation of the input and output, a description is provided for each program. An important part of this is the section "Structure of the Program", which offers the reader the possibility of program analysis. While this part of the description of the program is excellent in the case of LAOCN3, it is too short in the description of the other programs. All the programs have been tested independently, so that any errors are only of a formal nature. Thus on page 22 we should have "last two cards are blank". Similarly, on page 24, a blank card is missing between the data groups on the right half. The variable ISUM (p. 29) is equal to the number of β spins that are increased by 1.

All the programs can be purchased on a program tape, and the lists and cards have also been obtainable from the Quantum Chemistry Program Exchange (QCPE), Indiana University, Bloomington. However, even punching out the program lists bears no comparison with devising a new program as far as the time required is concerned, quite apart from the didactic value of a successful program analysis to the worker.

Günter Ege [NB 949 IE]

Kunststoff-Bestimmungsmöglichkeiten (Methods for the Analysis of Plastics). By *A. Krause* and *A. Lange*. Carl Hanser Verlag, München 1970. 2nd ed., 191 pp., 34 Tables, bound DM 38.—[1].

The aim of the authors is to present the methods most commonly used in practice for the qualitative and quantitative chemical analysis of plastics, including simple physicochemical tests such as the determination of density and refractive index. More complicated physicochemical methods such as IR, UV, and NMR spectroscopy or pyrolysis gas chromatography are not included.

Starting with the behavior of the plastics when heated in an ignition tube and in an open flame and the determination of density, solubility, softening point and melting point, refractive index, acid number, iodine number, etc., qualitative and quantitative methods are described for the determination of characteristic elements. After limiting the possibilities in this way, the special qualitative and quantitative methods for the individual plastics are then described. The book ends with a short section on the analysis of additives, particularly plasticizers, and a section on quality and acceptance tests with lists of the DIN standards and relevant reports in the Bundesgesundheitsblatt.

The strength of the book lies in the deliberate restriction of the subject matter to simple methods, particularly of a chemical nature; this is especially true in view of the large number of more complicated physicochemical methods and the work that they involve. The listing of characteristics in tabular form makes the book easier to use. A critical appraisal of the special qualitative and quantitative methods would have been of interest to the occasional user. The book can be used by anyone who is familiar with the fundamentals of analysis.

Ernst Klesper [NB 953 IE]

Contraception: The Chemical Control of Fertility. By *D. Lednicer*. Marcel Dekker, Inc., New York 1969. 1st ed., xiv, 296 pp., $ 13.75.

The book, whose six chapters are by authorities of excellent repute, presents an informative review based on about 700 references, and is outstanding in its clear arrangement. As an introduction to the rather heterogeneous material, the first chapter deals with the endocrinology of the female body, with special reference to control by the pituitary and the hypothalamus. The subsequent sections discuss the biology, pharmacology, chemistry, and testing of the contraceptives, which are grouped for discussion into steroid and nonsteroid compounds.

In the biological chapters, the effects produced by gestagens and estrogens are described in detail and summarized in tables; the results observed in animals are compared with the clinical findings for human subjects. Current views on the mode of action and the possible sites of action of the contraceptives and of their individual components are also discussed in this connection. The chemical chapters present a survey of the structural formulas and of the synthesis paths. Starting with the classical steroids, the many modifications (substitution, configuration) that have led to the various contraceptives are described. The final chapter contains information on the testing and screening methods, which are grouped according as the effects tested are central or peripheral.

The present monograph provides an excellent introduction to a field whose intensive scientific investigation is of the greatest interest to the further development of mankind. Its special value lies in the fact that on the one hand it acquaints biologists, biochemists, and pharmacologists with the problems of the chemical synthesis of contraceptives, while on the other it makes it easier for the chemist to evaluate pharmacological test results and clinical findings.

Heinz Breuer [NB 957 IE]

Methoden der Organischen Chemie (Methods of Organic Chemistry). (Houben-Weyl), Vol. V, Part 1a: Alkanes and Cycloalkanes, excluding Cyclopropane and Cyclobutane Derivatives. Edited by *Eugen Müller*. Georg Thieme Verlag, Stuttgart 1970. 4th ed., xxciii, 692 pp., 8 Figs., 83 Tables, bound DM 252.—.

The present volume[1] on the preparation of alkanes and cycloalkanes has undoubtedly been long awaited by many chemists in industry and in technical colleges as an im-

[1] Cf. Angew. Chem. internat. Edit. 5 (1966).

[1] Cf. Angew. Chem. internat. Edit. 9 (1970).

portant part of the set. This volume presents all the methods for the preparation of definite hydrocarbons of this type; the industrial methods for the production of hydrocarbon mixtures are not discussed systematically here. The exclusion of the cyclopropane and cyclobutane derivatives from the discussion of the cycloalkanes is justifiable in view of the special character of these ring systems. In my opinion, however, it would have been better to include the *hydrocarbons* having these ring systems, as this would have allowed the demonstration of the limitations of the various preparation methods when applied to small rings.

Among the arylalkanes, only hydrocarbons whose alkyl residue contains at least five carbon atoms are discussed, the others being dealt with in the volume on aromatic hydrocarbons. This division is doubtlessly a compromise, which, though it breaks the system, seems convenient and logical.

Nearly half of the volume (290 pages) is devoted to the reduction methods for the preparation of hydrocarbons. In addition to the text, a large amount of data is presented in very comprehensive tables. This is followed by a chapter on the solvolysis of organometallic compounds and isomerization reactions for the preparation of hydrocarbons. Besides a short chapter on the preparation of hydrocarbons by degradation reactions, there is a comprehensive chapter on synthesis methods. The chapter on the preparation of stereoisomeric hydrocarbons is particularly well written. The volume ends with an important chapter on the synthesis of labeled hydrocarbons.

The volume benefits from the fact that all the chapters were written by the same authors. It therefore gives an impression of unity. The profound experience of the authors is frequently evident, and the consequent critical evaluation of the methods makes the book particularly valuable to the user. On the whole, this volume is a valuable and well-presented addition to the set.

Hermann Stetter [NB 958a IE]

Methoden der Organischen Chemie (Methods of Organic Chemistry) (Houben-Weyl), Vol. V, Part 1c: Hydrocarbons Part 3. Edited by *Eugen Müller*. Georg Thieme Verlag, Stuttgart 1970, 4th ed., ix, 1296 pp., DM 458.—.

The present volume deals with the methods for the preparation and transformation of conjugated dienes. It shows the impossibility of adhering rigorously to an arrangement based on "Methods for the Preparation of Certain Organic Compounds", in view of the decades over which the publication of the parts of this handbook extends.

The first 854 pages are concerned with the preparation of dienes, and in breach of the system it deals not only with hydrocarbons containing conjugated double bonds but also with dienes containing functional groups.

The chapter on the transformation of the dienes is also very large covering a total of 285 pages. It must be pointed out, however, that a particularly large amount of space is devoted to the Diels-Alder diene synthesis.

As a result of the deviations from the system, this part to a very large degree assumes the character of a monograph, and could undoubtedly be used as a handbook independently of the other volumes.

The synthesis methods described are grouped according to whether or not the formation of the conjugated double bonds is accompanied by alteration of the carbon skeleton. This is followed by a chapter on the preparation of dienes from heterocyclic compounds and one on the purification, analysis, and handling of dienes.

The second part contains the following chapters: Oxidations, Additions without Formation of New Carbon-Carbon Bonds, Additions with Formation of New Carbon-Carbon Bonds, Cycloadditions, Photochemical Reactions, Dehydrogenations and Disproportionations, Substitutions, Isomerizations, Reactions of Cyclopentadiene with Metal Compounds.

Next comes the long chapter on the Diels-Alder reaction. Both the preparation method and the reactions of the dienes are presented very comprehensively and systematically. The volume is of great practical value because of the many typical and well-chosen examples, which are supplemented by tables. The excellent chapter on the Diels-Alder reaction deserves special praise.

To conclude, it may be stated that this well-written volume is an important and necessary addition to the set as a whole for all chemists working in technical colleges and in industry

Hermann Stetter [NB 958 b IE]

Kunststoffe I und II, Aufbau und Eigenschaften – Kunststoffsorten – Anwendungen T 7, Kunststoffverarbeitung T8 (Plastics I and II, Structure and Properties – Types of Plastics – Applications T7, Plastics processing T8). By *H. Domininghaus*. VDI-Taschenbücher 1969. 1st Edit. T7: 196 pp., 106 illustrations, 13 tables, DM 11.80; T8: 138 pp., 65 illustrations, 2 tables, DM 11.80.

These two volumes are intended to be an introduction to synthetic materials for users and consumers and also for students in specialist fields. The first part deals with the structure and properties of plastics, the more important types being discussed from the point of view of chemical structure, behavior, and applications, as well as with commercial products. A special section summarizes the most important fields of application and also economic and historical data. The second part is concerned with the methods of processing plastics (preparation, calendering, production of coatings, foams, compression molding, injection molding, extrusion, forming, decoration), and operational problems are discussed. Finally, there is a bibliography, rather arbitrary and not very representative, and a subject index.

The book is certainly a suitable introduction to plastics, particularly for engineers who are mainly interested in the technology of processing. However, the first volume not only contains a large number of printing errors, but also a number of chemically ambiguous formulations which are consequently open to misinterpretation. Thus, in the treatment of the types of polymerization it would be desirable to have a simple system of formulas, and this would certainly have helped to clarify the text. If there is to be another edition the chemical section will need careful revision, since there are also a number of factual errors.

Finally, in the case of the more important properties at least, one would have welcomed some indication of how these properties were defined and measured; the reader will search the subject index in vain for the modulus of elasticity, tensile strength, or thermal stability, although these concepts are used in many places and numerical values are given for them. Anyone who wants to be informed on such fundamental matters will do better to turn to more detailed

presentations. However, the second part of the work can be heartily recommended as an introduction to plastics processing, particularly as the author has made full use of his extensive practical experience.

Dietrich Braun [NB 962 IE]

Festkörperdosimetrie ionisierender Strahlung (Solid State Dosimetry of Ionizing Radiation). By *M. Frank* and *W. Stolz*. Verlag Chemie, Weinheim 1969. 1st Edit., 283 pp., 97 illustrations, 28 tables, DM 48.—.

Ionizing radiation can induce numerous physical and chemical modifications in solid bodies, and the nature and the extent of these modifications enable conclusions to be drawn about the radiation energy absorbed by the solid body. In turn, this enables overall radiation dosage determinations.

This phenomenon has been much studied over the last 20 years particularly in solid state physics, resulting in a large number of publications on this topic. The present book by *Frank* and *Stolz* is the first monograph to be published in German. After an introduction into the general theoretical basis of dosimetry, the methods of integrating solid state dosimetry are described. These include dosimetry by means of thermoluminescence, radiophotoluminescence, exoelectron emission, luminescence decay, coloration of crystals and plastics, and also by means of solid state track detectors. The authors then deal with the methods of scintillation dosimetry and of dosimetry based on radiation-induced changes in conductivity. For each method there is a description of the underlying physical effects and the supporting mathematics, and experimental details of the method are then given together with practical applications. The rapidity with which this field is developing makes a new and amplified edition of this book desirable even at this stage. This is particularly true of the very short chapter on dosimetry using exoelectron emission and solid state track detectors, since a large number of publications on these topics have appeared in the short time since the book was published.

The authors explain in their preface that the book is intended for all those concerned with the problems of dosage measurement in radiation protection, radiation therapy, and radiobiology, and also in work with accelerators, reactors, and other units using radiation. The reviewer would also recommend this book, because of its precise mode of expression and the excellent presentation of the facts, to all students who are thinking of working in one or more of the fields discussed.

J. Hacke [NB 961 IE]

Infrared Spectroscopy. Experimental Methods and Techniques. By *J. E. Stewart*. Marcel Dekker Inc., New York 1970. 1st Edit., 636 pp., numerous illustrations, $ 36.50.

The perfection with which commercial IR instruments are now manufactured in the widest possible range of types has led to IR spectroscopy becoming a method in which the user – particularly in the case of chemists – is as a rule interested only in the possible range of applications and not in the constructional details. This situation is reflected in the literature on the subject. It is all the more pleasant to find in the present volume a very wide-ranging survey of the fundamentals of the construction of modern IR instruments.

The book contains all the essential information on the basic theory of the equipment and on the construction of IR instruments (optical systems and their components, electronic components, detectors, *etc.*), and a wide range of commercially available instruments is surveyed. In individual chapters descriptions are given of interference spectroscopy, absorption, reflection, and emission measurement methods, and also of the constructional basis for more recent applications (study of samples under extreme conditions *etc.*). Each chapter has a bibliography, in some cases very extensive. There is also an author index (7 pages) and a subject index (13 pages).

The book is intended for the specialist concerned with the instrumental problems of IR spectroscopy, and it should prove an important source of information. It should, however, be in the library of all institutions that use IR spectroscopy in any form, so that anyone who regards his spectroscope as more than just a "black box" will have the opportunity of learning more about his equipment as the need arises.

Egon Fahr [NB 963 IE]

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Synthesis and Reactions of Ketenimines[**]

By Grant R. Krow[*]

Ketenimines $R^1R^2C{=}C{=}N{-}R^3$ *were first reported in 1919, but the development of the chemistry of these compounds is of relatively recent origin. These heterocumulenes are becoming of increasing interest as a dehydrating agent for peptide syntheses, as a coreagent in dimethyl sulfoxide oxidations, and as a substrate in the synthesis of heterocycles by condensation with polar multiple bonds and dipolar systems. The cycloadditions are of special interest from the viewpoint of orbital symmetry considerations. Some unusual organometallic complexes of ketenimines have also been synthesized. Recently some triaryl ketenimines have been found to have insecticidal and miticidal activity. Polymeric ketenimines have been implicated as molecular precursors of life.*

1. Introduction

Ketenimines can be represented by the resonance structures *(1)* and *(2)* which emphasize the nucleophilic properties of the heteroatom and the β-carbon atom, and by structure *(3)*, which accounts for the electrophilic nature of the α-carbon atom.

$R_2C{=}C{=}\ddot{N}{-}R$ $\quad$ $R_2\ddot{C}{-}C{\equiv}\overset{\oplus}{N}{-}R$ $\quad$ $R_2C{=}\overset{\oplus}{C}{-}\ddot{N}{-}R$

(1) $\quad$ *(2)* $\quad$ *(3)*

Under those circumstances where structure *(2)* makes a large contribution to the resonance hybrid, ketenimines will be similar in properties to enamines *(4)* and ynamines

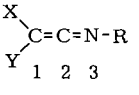
$R_2C{=}CH{-}NR_2$ $\quad$ $RC{\equiv}C{-}NR_2$ $\quad$ $R_2C{=}C{=}O$

(4) $\quad$ *(5)* $\quad$ *(6)*

(5). As resonance form *(3)* increases in importance, ketenimines will react similarly to ketenes *(6)*.

2. Stability and Principles of Synthesis

Most ketenimines are colorless or pale yellow oils or low melting solids, distillable at high vacuum. The infrared spectra exhibit characteristic cumulene absorption at 2000–2050 cm^{-1}. The smaller trialkylketenimines resinify easily and have not been isolated in pure form. Ketenimines are known with *N*-alkyl, -aryl, -hydrogen, -phosphorus, -nitroso, and -boron substituents and having N—Sn, N—Si, and N—Ir bonds. Substituents present on the carbon have been alkyl, aryl, hydrogen, trifluoromethyl, trimethylsilyl, ethoxycarbonyl, cyano, sulfonyl, phosphoranylidene, and carbonyl groups. Stable ketenimines with amino, alkoxy, or thioether substituents directly bonded to either the ketene or imine portions have not yet been synthesized; nor have *N*-halo, *N*-ethoxycarbonyl-, or *N*-sulfonylketenimines been reported.



For purposes of the present discussion the syntheses of ketenimines have been divided into four classes in which

(i) the terminal groups =CXY or =NR are formed by substitution reactions utilizing heterocumulenes (Section 3);

(ii) the ketenimine group (atoms 1–3) supplied as a nitrile anion or nitrile radical is substituted on nitrogen (Section 4);

(iii) the carbimino group (atoms 2, 3), supplied as an isocyanide, is added to atom 1, supplied *via* an acetylene, cyclopropenone, or carbene (Section 5);

(iv) a molecule containing a linear sequence of atoms (atoms 1–3) is converted into a ketenimine by an elimination reaction, an intramolecular rearrangement, or an

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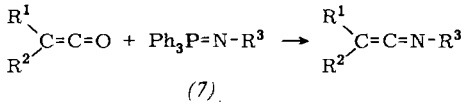
[**] The designation "ketenimine" has been adopted by Chemical Abstracts. The compounds are named as 1-alkenylideneamines in the IUPAC rules for the nomenclature of organic compounds.

elimination-rearrangement. The rearrangement reactions involve migration of a substituent from what will ultimately be the central carbon (atom 2) of the ketenimine to the nitrogen of the ketenimine (Section 6–8).

3. Ketenimines from Ylides by Substitution in Heterocumulenes

3.1. Substitution in Ketenes

The oxygen of a ketene can be replaced by a substituted imino function. *Staudinger*[1] investigated the reactions of various ketene derivatives with triphenyliminophosphorane *(7)*; although yields were not specified, ketenimines prepared in this manner are listed in Table 1.

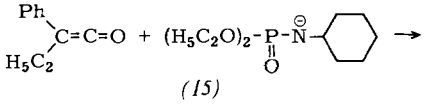


(7)

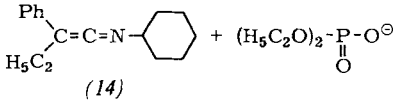
Table 1. Ketenimines $R^1R^2C{=}C{=}N{-}R^3$ prepared form ketenes.

	Ketenimine R^1	R^2	R^3	Physical properties	Ref.
(8)	Ph	Ph	Ph	yellow, crystalline	[1]
(9)	Ph	Ph	CH_3	yellow, liquid	[1]
(10)	H	H	Ph	colorless (polymerizes)	[1]
(11)	$COOC_2H_5$	$COOC_2H_5$	Ph	colorless, crystalline	[1]
(12)	CH_3	CH_3	Ph	green, oil	[1]
(13)	H	H	C_2H_5	(polymer only)	[1]
(14)	Ph	C_2H_5	C_6H_{11}	oil	[2]

Dialkylphosphoramidate anions *(15)* also react with ketenes to form ketenimines. By this route *Wadsworth* and *Emmons*[2] prepared phenyl(ethyl)-ketene-*N*-cyclohexylimine *(14)* in 58% yield.

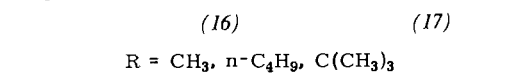


(15)



(14)

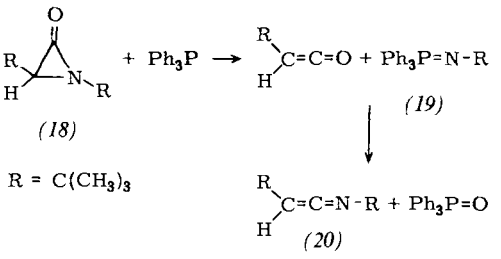
Recently *Raasch*[3] has synthesized the antistatic agents bis(trifluoromethyl)ketene-*N*-alkylimines *(17)* by reaction of bis(trifluoromethyl)thioketene with the formal ylides dialkylsulfur diimides *(16)*.



(16) *(17)*

R = CH_3, n-C_4H_9, $C(CH_3)_3$

In a somewhat novel reaction *Bergmark* and *Corcoran*[4] have found di-*tert*-butylaziridinone *(18)* to react with triphenylphosphane to give *tert*-butylketene-*N*-*tert*-butylimine *(20)* in unspecified yield, probably *via* intermediate *tert*-butylketene and the iminophosphorane *(19)*.



(18)

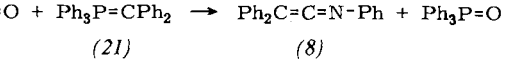
R = $C(CH_3)_3$

(19)

(20)

3.2. Substitution in Isocyanates

In their initial reports on the synthesis of ketenimines, *Staudinger* and *Meyer*[5] in 1920 reacted phenyl isocyanate with diphenylmethylenetriphenylphosphorane *(21)* to prepare ketenimine *(8)*[6].



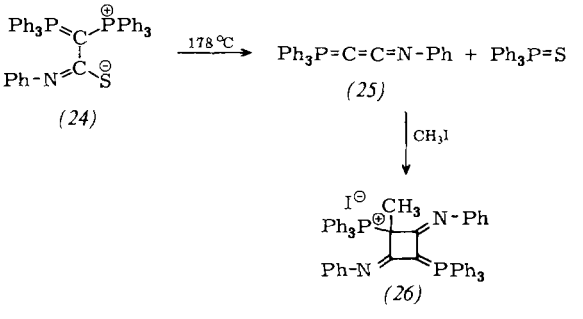
(21) *(8)*

The ylide route has been especially effective in the synthesis of heterocumulenes. A cumulene ylide *(22)* has been used by *Ratts* and *Partos*[7] to prepare a cumulene imine *(23)* (isolated as its amide) from methyl isocyanate.



(22) *(23)*

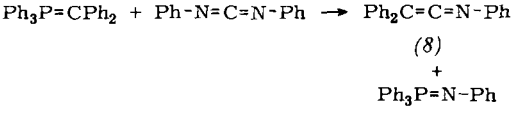
Birum and *Mathews*[8] have prepared the unique compound *(25)*, which can be regarded as a cumulene ylide and as a ketenimine, by thermal cleavage of the phosphonium inner salt *(24)* prepared from hexaphenylcarbodiphosphorane and phenyl isothiocyanate. Ketenimine *(25)* was identified by its 5.0 μm infrared band and by conversion into a cyclic dimer *(26)* with methyl iodide.



(24) *(25)* *(26)*

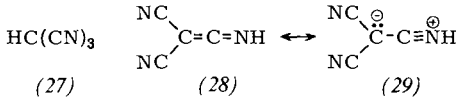
3.3. Substitution in Carbodiimides

When stirred at 160–180 °C for 4 h diphenylmethylenetriphenylphosphorane and diphenylcarbodiimide undergo ylide exchange. Diphenylacetanilide, the hydrolysis product of triphenylketenimine *(8)*, was isolated in 94% yield[9].



4. Ketenimines *via* Nitrile Derivatives

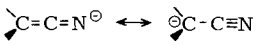
Nitriles containing α-hydrogens can be considered as tautomers of ketenimines. Although the tautomeric equilibrium usually favors the nitrile, *Trofimenko*[10a] has reported that cyanoform *(27)* exists as dicyanoketenimine *(28)*. Resonance forms such as *(29)* probably stabilize the ketenimine structure[10b].



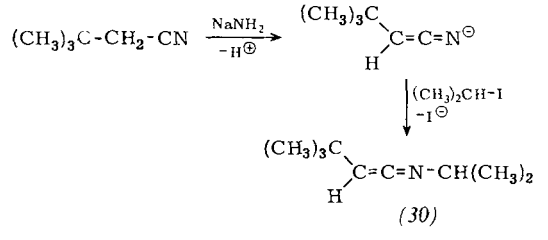
(27) *(28)* *(29)*

4.1. Alkylation of Nitrile Anions

A variety of ketenimines have now been prepared *via* substitution reactions of ambident nitrile anions on nitrogen. Although alkylation of this ambident ion generally

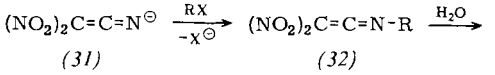


occurs on carbon, *tert*-butylketene-*N*-isopropylimine *(30)* has been isolated[11] in 56% yield on *N*-alkylation of the sterically hindered *tert*-butylacetonitrile anion with the bulky isopropyl iodide as alkylating agent.

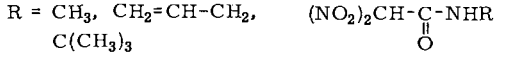


(30)

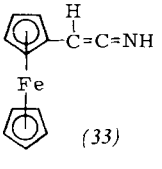
Similarly, *N*-alkylation of the dinitroacetonitrile anion *(31)* with organic halides has been found[12] to give amides arising from ketenimines *(32)*.



(31) *(32)*



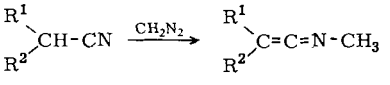
Dewey[13] has synthesized the stable ferrocenylketenimine *(33)*, which is protonated on nitrogen, by treatment of ferrocenylacetonitrile anion with methylmagnesium chloride in ether and subsequent addition of methanol. Compound *(33)* exhibits a strong ketenimine absorption at 2185 cm^{-1}. Normal aromatic ketenimines absorb at 2002–2016 cm^{-1}.



(33)

Treatment of a nitrile substituted by strongly electron-withdrawing *alpha* substituents with diazomethane generates a nitrile anion. *N*-Alkylation of such an anion by the methyldiazonium ion yields a ketenimine. Ketenimines thus prepared by *Dijkstra* and *Backer*[14] are shown in Table 2.

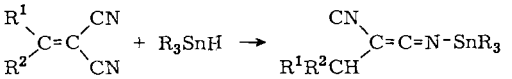
Table 2. Ketenimines prepared from nitriles with diazomethane [14].



	R^1	R^2
(34)	SO_2CH_3	SO_2CH_3
(35)	SO_2CH_3	SO_2Ph
(36)	SO_2CH_3	$COOC_2H_5$
(37)	SO_2Ph	SO_2Ph

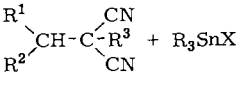
4.2. *N*-Substitution of Nitrile Anions by Heteroatoms

Tin: Nitriles have been used as precursors for preparing *N*-stannylketenimines. Polar 1,4 addition of a trialkyltin hydride *(39)* to an alkylidenemalononitrile *(38)* results in formation of an *N*-trialkylstannylketenimine *(40)*.



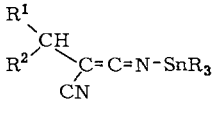
(38) *(39)* *(40)*

It is possible to modify this reaction by using an alkylmalononitrile and a trialkylstannyldiethylamine *(41)*, a sodium alkylmalononitrile and a trialkyltin chloride *(42)*, or an α-bromoalkylmalononitrile and a lithiotrialkyltin compound *(43)*. Some *N*-stannylketenimines prepared[15] are shown in Table 3.



	R^3	X
(41)	H	$N(C_2H_5)_2$
(42)	Na	Cl
(43)	Br	Li

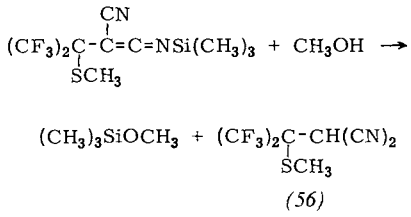
Table 3. Types of *N*-trialkylstannylketenimines prepared [15].



	R^1	R^2
(44)	Ph	H
(45)	CH_3	H
(46)	C_2H_5O	H
(47)	Ph	Ph
(48)	Ph	CH_3
(49)	CH_3	CH_3
(50) [a]	H	H
(51)	——$(CH_2)_5$——	
(52)	Ph—CH=CH—	H
(53)	CN	CN
(54)	*p*-$(CH_3)_2N$—Ph	CN

[a] Polymerizes readily.

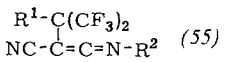
Silicon, boron, tin: The synthesis of ketenimines by 1,4-addition to α,β unsaturated dinitriles has been extended by *Abel, Crow*, and *Wingfield*[16]. A formal 1,4 insertion reaction of 1,1-bis(trihalogenomethyl)-2,2-dicyanoethylene into a variety of tin, silicon, and boron bonds (Table 4) has



(56)

been shown to generate ketenimines *(55)* under mild conditions. With the exception of some of the *N*-trialkylstannylketenimines, all the products undergo rapid alcoholysis and hydrolysis, the non-metalloid product reverting to the dicyano form *(56)*.

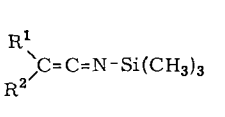
Table 4. Ketenimines *(55)* *via* insertion reactions of $(CF_3)_2C{=}C(CN)_2$ [16].



(55)

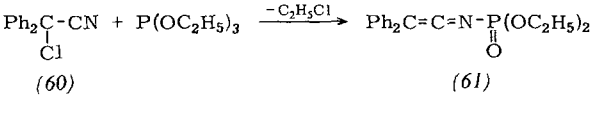
Organometallic cpd.	*(55)* R^1	R^2
$(CH_3)_3Si{-}SCH_3$	SCH_3	$Si(CH_3)_3$
$(CH_3)_3Si{-}NHPh$	NHPh	$Si(CH_3)_3$
$(CH_3)_3Si{-}H$	H	$Si(CH_3)_3$
$(CH_3)_3Sn{-}SCH_3$	SCH_3	$Sn(CH_3)_3$
$(CH_3)_3Sn{-}CH_2{-}CH{=}CH_2$	$CH_2{=}CH{-}CH_2$	$Sn(CH_3)_3$
$(CH_3S)_3B$	SCH_3	$B_{1/3}$
$[(CH_3)_2N]_3B$	$N(CH_3)_2$	$B_{1/3}$

Silicon: *Krüger* and *Rochow*[17] have prepared the *N*-silylketenimine *(57)* by reaction of sodium bistrimethylsilylamide with acetonitrile at −60 to +30 °C, followed by treatment of the ether-insoluble nitrile anion with trimethylchlorosilane. Mono- and diphenylacetonitrile gave ketenimines *(58)* and *(59)*, respectively.



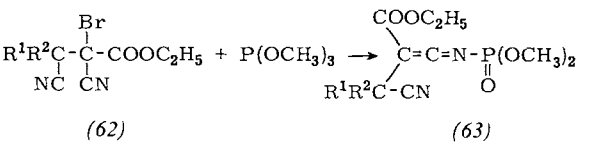
	R^1	R^2
(57)	$(CH_3)_3Si$	$(CH_3)_3Si$
(58)	$(CH_3)_3Si$	Ph
(59)	Ph	Ph

Phosphorus: *Partos* and *Speciale*[18] found that reaction of chlorodiphenylacetonitrile *(60)* with triethyl phosphite results in formation of an *N*-phosphorus-substituted ketenimine *(61)*.



(60) *(61)*

N-Phosphorusketenimines *(63)* were also obtained[19] when trimethyl phosphite was reacted with α-bromo-α,β-dicyanopropionates *(62)*. Some ketenimines prepared in this way are shown in Table 5.



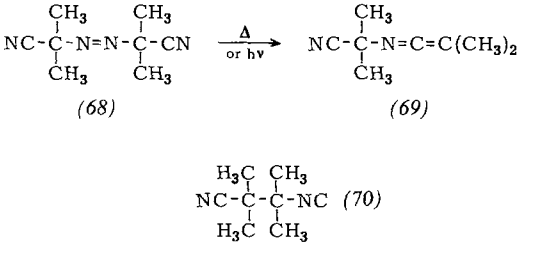
(62) *(63)*

Table 5. *N*-Phosphorusketenimines of type *(63)* prepared [19]

	R^1	R^2
(64)	Ph	Ph
(65)	$PhCH_2$	$PhCH_2$
(66)	Ph	CH_3
(67)	Ph	C_2H_5

4.3. Alkylation of Nitrile Radicals

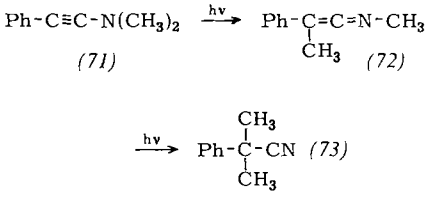
Dimerization of the thermal or photochemical decomposition products[20] of 2,2-azobis(isobutyronitrile) *(68)* results in formation of a small amount of ketenimines *(69)* as well as the normal product, tetramethylsuccinodinitrile *(70)*. Both products arise from isobutyronitrile radicals, *(69)* from combination of a carbon and nitrogen radical, *(70)* from combination of two carbon radicals.



(68) *(69)*

(70)

Selvarajan and *Boyer*[21] have recently identified ketenimines as products of unsensitized irradiation at 254 nm of *N,N*-dimethyl(phenylethynyl)amine *(71)* in cyclohexane. Ketenimine *(72)*, identified by its 2020 cm^{-1} band in the crude photolyzate, is an assumed intermediate in the formation of α-phenylisobutyronitrile *(73)*.



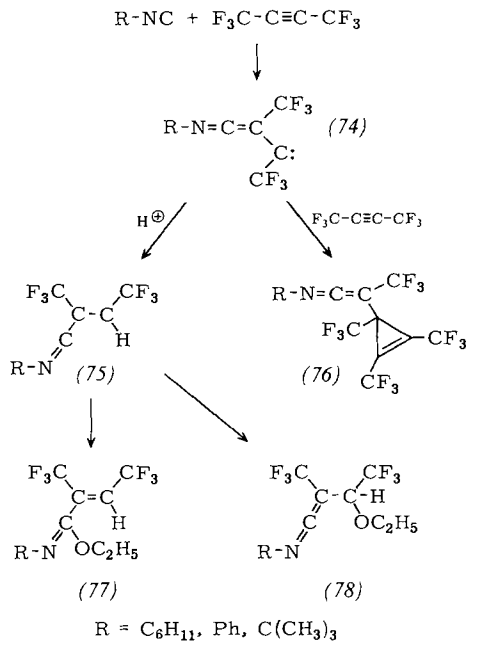
(71) *(72)*

(73)

5. Ketenimines from Addition Reactions of Isocyanides

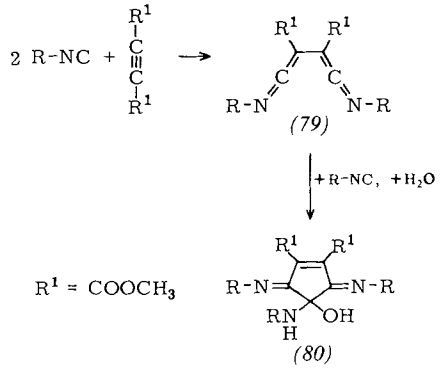
5.1. Addition of Isocyanides to Alkynes

Oakes, David, and *Nagel*[22] have found 2:1 adducts of hexafluoro-2-butyne and isocyanides formed in inert solvents to have the cyclopropenyl ketenimine structure *(76)*. Identified by a ketenimine cumulene absorption at 4.80 μm in their infrared spectra, the stable pale yellow



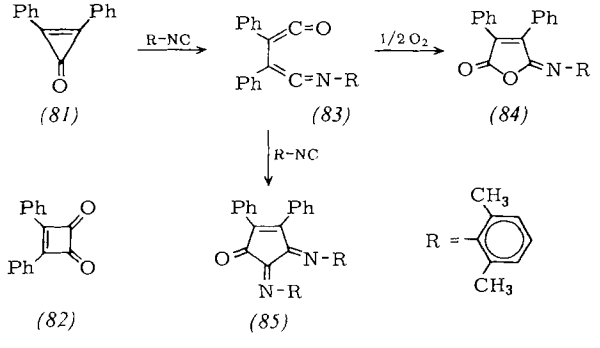
liquids conceivably are formed *via* the carbene *(74)*. In the protic solvent ethanol, ketenimine *(77)* is formed.

Takizawa and co-workers[23] have isolated the bisketenimine *(79)* in 3% yield as an intermediate in the reaction of an aryl isocyanide with dimethyl acetylenedicarboxylate.



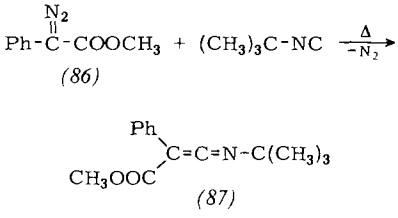
5.2. Addition of Isocyanides to Cyclopropenones

Takizawa[24] has also postulated a ketenimine intermediate in the reaction of diphenylcyclopropenone *(81)* with 2,6-dimethylphenyl isocyanide. The products *(84)* and *(85)* isolated from this reaction can be explained *via* the intermediacy of the "ketene-ketenimine" *(83)*. The same products result from addition of diketone *(82)* to 2,6-dimethylphenyl isocyanide.

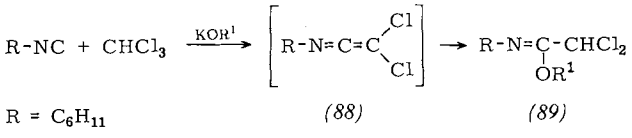


5.3. Addition of Isocyanides and Carbenes

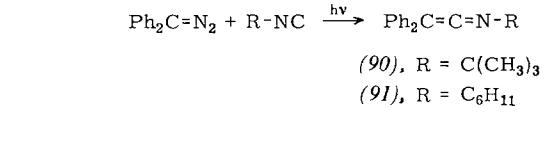
Ciganek[25] has shown that carbenes and isocyanides, two formally divalent species, can react to generate ketenimines. Thermolysis of methyl phenyldiazoacetate *(86)* in *tert*-butyl isocyanide gave ketenimine *(87)* in 51% yield.

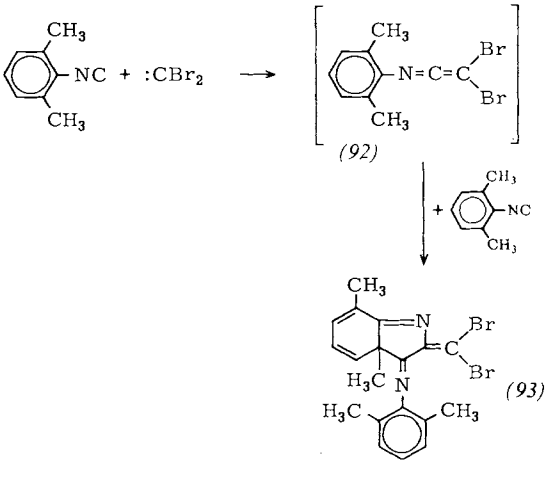


An earlier attempt[26] to prepare ketenimine *(88)* by reaction of dichlorocarbene (generated from potassium trichloroacetate in alcohol) with cyclohexyl isocyanide gave *N*-cyclohexyldichloroacetimidate *(89)*.



Boyer and *Beverung*[27] photolyzed diphenyldiazomethane at 2537 Å in the presence of cyclohexyl isocyanide to form *N*-cyclohexyldiphenylketenimine *(91)*. Absorption at 4.90 μm identified the ketenimine, which was isolated in 50% yield as its amide. *Green* and *Singer*[28] prepared ketenimines *(90)* and *(91)*, in 25—30% and 45—50% yields respectively, by the same method.





Takizawa and *Obata*[24] have observed 2,6-dimethylphenyl isocyanide to react with dibromocarbene to yield indolenine derivatives *(93)*. The intermediacy of ketenimine *(92)* is postulated in order to explain this result.

6. Ketenimines *via* Simple Elimination Reactions

6.1. Dehalogenation of α-Chloro Imidoyl Chlorides

Stevens and *French*[29] found that α-chloro imidoyl chlorides *(94)*, which are readily synthesized from amides, can be dehalogenated with sodium iodide in acetone. Although the dehalogenation method fails to produce ketenimines with dialkyl substitution on carbon, the synthesis is successful for preparing diaryl-*N*-alkyl- and triarylketenimines. *p*-Nitrophenylketene-*N*-arylimines can be prepared by dehalogenation, but not by dehydrohalogenation (see Section 6.2). *Singhal*[30] has found that dehalogenation of α-chloro imidoyl chlorides can also be effected with copper metal at 20—50 °C. Zinc fails to dehalogenate α-chloro imidoyl chlorides, however.

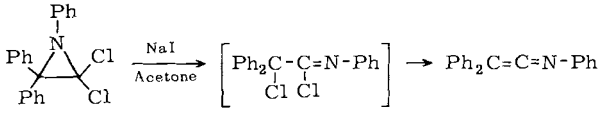
$$Ph_2CH\text{-}\underset{\underset{O}{\|}}{C}\text{-}NHPh \xrightarrow{2\ PCl_5} Ph_2\overset{\overset{Cl}{|}}{C}\text{-}\overset{\overset{Cl}{|}}{C}\text{=}N\text{-}Ph$$

(94)

$$\xrightarrow[Acetone]{NaI} Ph_2C\text{=}C\text{=}N\text{-}Ph$$

(8)

A recent variant of the above procedure[31] utilizes dichloroaziridines, prepared by reaction of imines with dichlorocarbene, as precursors of α-chloro imidoyl chlorides. Refluxing the dichloroaziridine *(95)* with sodium iodide in acetone generates triarylketenimine *(8)* in excellent yields.



(94a) *(94)* *(8)*

6.2. Dehydrohalogenation of Imidoyl Chlorides

Stevens and *French*[32] found that imidoyl chlorides *(95)* bearing a single *alpha* hydrogen atom can be dehydrohalogenated to ketenimines *(8)* by means of triethylamine. The yields by this route have been improved[33a] using triphenylphosphine, bromine, and triethylamine in refluxing dichloromethane. This approach is especially useful

$$Ph_2CH\text{-}\underset{\underset{O}{\|}}{C}\text{-}NHPh \xrightarrow{PCl_5} Ph_2CH\text{-}\overset{\overset{Cl}{|}}{C}\text{=}N\text{-}Ph$$

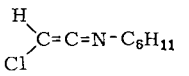
(95)

$$\xrightarrow{(C_2H_5)_3N} Ph_2C\text{=}C\text{=}N\text{-}Ph$$

(8)

for ketenimines with dialiphatic substitution on the ketene portion of the cumulene and the dehydrohalogenation method has been used[33b] to prepare a diethoxycarbonyl-substituted ketenimine *(96)*, and reportedly the unstable chloroketenimine *(97)*[52].

$(H_5C_2OOC)_2C\text{=}C\text{=}N\text{-}Ph$ *(96)*



(97)

In Table 6 is shown a comparison made by *Stevens* and *French*[32] of the dehydrochlorination and dechlorination procedures for the synthesis of ketenimines. The dehydrochlorination procedure was superior except in the case of diphenylketene-*N*-methylimine *(100)*.

Table 6. Comparison of syntheses of ketenimines ($R^1R^2C\text{=}C\text{=}N\text{—}R^3$) carried out by *Stevens* and *French* [32].

	R^1	R^2	R^3	Yield (%) (based on starting amide) dehydrochlorination	dechlorination
(98)	CH_3	CH_3	*p*-tolyl	58.0	0
(99)	*n*-C_4H_9	C_2H_5	*n*-C_4H_9	57.0	—
(100)	C_6H_5	C_6H_5	CH_3	2.4	42
(101)	C_6H_5	C_6H_5	*n*-C_4H_9	69.0	63
(102)	C_6H_5	C_6H_5	*p*-tolyl	65.0	56

6.3. Dehydration of Secondary Amides

Stevens and *Singhal*[34] found that dehydration of secondary amides with phosphorus pentoxide and pyridine is a useful method for preparing triarylketenimines such as *(8)*,

$$Ph_2\text{-}CH\text{-}\underset{\underset{O}{\|}}{C}\text{-}NHPh \xrightarrow[Pyridine]{P_2O_5} Ph_2C\text{=}C\text{=}N\text{-}Ph$$

(8)

except when the *N*-aryl group contains a strongly electron-withdrawing substituent such as the *p*-nitro group. The dehydration procedure is successful also for preparing diarylketene-*N*-*n*-alkylimines. A list of diphenylketene-*N*-aryl(or *N*-alkyl)imines prepared by *Stevens* and *Singhal*[34] appears in Table 7.

Table 7. Diphenylketene-*N*-aryl(alkyl)imines $Ph_2C\text{=}C\text{=}N\text{—}R$ prepared by *Stevens* and *Singhal* [34] using the dehydration procedure.

	R	Yield (%)
(102)	*p*-CH_3—C_6H_4	87
(103)	*p*-Br—C_6H_4	69
(104)	*p*-H_3CO—C_6H_4	69
(105)	*o*-CH_3—C_6H_4	84
(106)	*p*-H_3CS—C_6H_4	75
(107)	*o*-H_3CO—C_6H_4	67
(108)	*n*-C_4H_9	50
(109)	*p*-NO_2—C_6H_4	0
(110)	*p*-H_3CSO_2—C_6H_4	30
(111)	*tert*-C_4H_9	0

The dehydration procedure can be modified by converting the amide first into a thioamide and treating this with mercuric oxide[35]. In another variation, *Singer* and *Davis*[36]

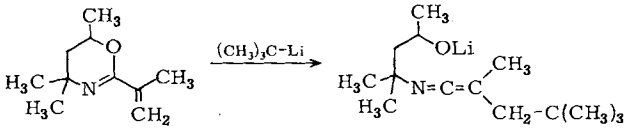
utilized triethylamine instead of pyridine as base in order to prepare a trialkylketenimine. A list of ketenimines prepared by *Singer* and *Davis* appears in Table 8. The dehydration procedure is inferior to the dehydrohalogenation procedure for all-aliphatic and dialiphatic *N*-aromatic ketenimines.

Table 8. Ketenimines $R^1R^2C{=}C{=}N{-}R^3$ prepared by *Singer* and *Davis* [36] using the dehydration procedure.

	R^1	R^2	R^3	Yield (%)
(112)	CH_3	CH_3	C_6H_{11}	18
(113)	CH_3	CH_3	C_6H_5	20
(114)	C_2H_5	C_6H_5	*sec*-C_4H_9	20
(115)	C_2H_5	C_6H_5	C_6H_5	20
(116)	C_6H_5	C_6H_5	*sec*-C_4H_9	25—30
(8)	C_6H_5	C_6H_5	C_6H_5	25—30

6.4. Ring Opening of 2-Vinyl-1,3-oxazines

Meyers and *Kovelsky*[37] have isolated a hygroscopic salt *(118)* from treatment of oxazine *(117)* with *tert*-butyllithium. Strong infrared absorption at 2010 cm^{-1} identified this salt as the ketenimine.

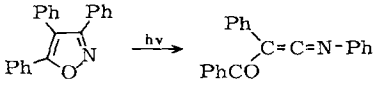


(117) *(118)*

7. Ketenimines by Rearrangement Reactions

7.1. Photolysis of Triarylisoxazoles

Schechter and *Kurtz*[38] have shown that irradiation of a triphenylisoxazole *(119)* with 3000-Å or 2537-Å light results in isomerization to benzoylphenylketene-*N*-phenylimine *(120)*. The yield of *(120)* was 40% and the method



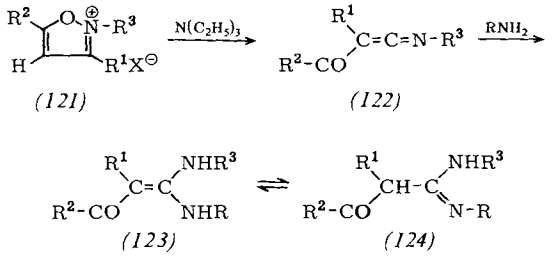
(119) *(120)*

represents a rapid and convenient way of preparing a ketoketenimine.

8. Ketenimines by Elimination-Rearrangement

8.1. Basic Decomposition of Isoxazolium Salts

N-tert-Butylisoxazolium salts *(121)* bearing hydrogen in the 4-position have been converted by *Woodward* and *Woodman*[39] into isolable ketoketenimines *(122)* by treatment of the salts with triethylamine. A bulky, branched substituent R^1 is not necessary for the success of the approach[40]. The yellow oily ketoketenimines, stable at 0 °C, were identified by characteristic infrared absorption for the cumulene linkage at 4.9 μm, and by their reaction with amines to form tautomeric acylketene aminals *(123)*



(121) *(122)*

(123) *(124)*

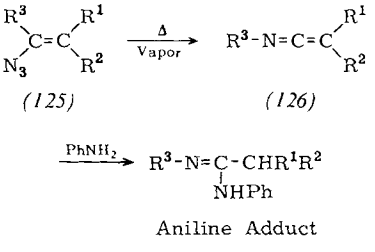
of acyl amidines *(124)*. *Olafson* and *Marino*[41] have recently reviewed the use of isoxazolium salts in peptide syntheses.

Table 9. Isolated ketoketenimines $R^2COC(R^1){=}C{=}N{-}R^3$ *(122)*.

R^1	R^2	R^3	Ref.
H	CH_3	*tert*-Butyl	[39]
CH_3	Ph	*tert*-Butyl	[39]
Ph	H	$CH(CH_3)Ph$	[40]
CH_3	Ph	CH_2Ph	[40]
CH_3	Ph	Ph	[40]
H	H	*tert*-Butyl	[40]

8.2. Photolysis or Pyrolysis of Vinyl Azides

Smolinsky[42] has inferred the formation of small amounts (<5%) of ketenimine *(126)* from infrared bands in the 4.9–5.0-μm region of a crude pyrolyzate obtained upon vapor-phase pyrolysis of vinyl azides *(125)*. *Friedrich*[43] has isolated HCl, ethanol, or aniline adducts of ketenimines formed by thermal decomposition of azides at 60–70 °C.



(125) *(126)*

Aniline Adduct

Of special interest is ketenimine *(130)*, the tautomer of cyanoform. The tetramethylammonium salt of *(130)* can be isolated if the reaction is carried out in acetone/water.

Table 10. Ketenimines $R^1R^2C{=}C{=}N{-}R^3$ *(126)* from vinyl azides.

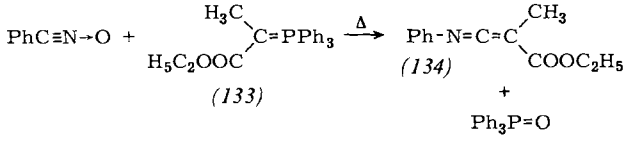
	R^1	R^2	R^3	Yield (%)	Ref.
(127)	H	H	Ph	5	[42] [a]
(128)	CN	CN	Ph	79	[43] [b]
(129)	CN	CN	CH_3	58	[43] [b]
(130)	CN	CN	H	61	[43] [b]
(131)	$COOC_2H_5$	H	CH_3	20	[44] [c]
(132)	$COOC_2H_5$	CH_3	CH_3	20	[44] [c]

[a] Identified by its 4.9—5.0 μm infrared band.
[b] Isolated as its HCl adduct.
[c] Identified by ketenimine infrared band at 4.87 μm.

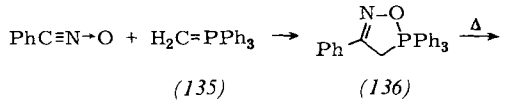
Harvey and *Ratts*[44] have also obtained ketenimines *(131)–(132)* in low yield by photolysis of vinyl azides. The ketenimines can be detected by the infrared band at 4.87 μm, but are destroyed during attempted distillation. A list of ketenimines prepared from vinyl azides appears in Table 10.

8.3. Reaction of Nitrile Oxides with Phosphorus Ylides

Bestmann and *Kunstmann*[45] found that benzonitrile oxide and ethoxycarbonylphosphorane *(133)* yielded ketenimine *(134)* in 68% yield when heated. *Huisgen* and *Wulff*[46] similarly formed ketenimine *(137)* when the



(133) *(134)*



(135) *(136)*

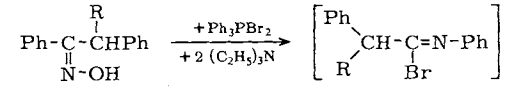
$H_2C{=}C{=}N{-}Ph + Ph_3P{=}O$

(137)

adduct *(136)* of benzonitrile oxide and methylenetriphenylphosphorane *(135)* was heated to 130 °C. Ketenimine *(134)* could be distilled; however, identification of ketenimine *(137)* was made through its aniline adduct.

8.4. Reaction of Ketoximes with Dibromotriphenylphosphorane and Base

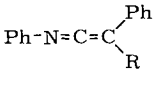
Masaki, *Fukui*, and *Ohta*[47] treated oxime *(138)* with dibromotriphenylphosphorane and two equivalents of triethylamine at room temperature in acetonitrile to generate



(138)

R = Ph, H

(139)



(140)

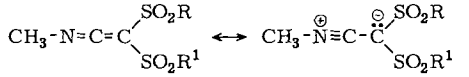
a ketenimine. The ketenimine probably arises by dehydrobromination of an intermediate imidoyl bromide *(139)*. When R is hydrogen, the yield of ketenimine *(140)* is 75%.

9. Physical Properties of Ketenimines

The ketenimine system is potentially axially dissymmetric in an analogous manner to allenes. The ability to observe axial dissymetry, however, depends upon the configurational stability of the ketenimine, which might invert its configuration either by rotation about the imine or inversion of the nitrogen lone pair. The calculated barrier to interconversion is $\leqslant 10$ kcal/mole[48] in agreement with available experimental evidence.

9.1. Structure by X-Ray Methods

X-ray studies[49–51] have shown that with strong electron-withdrawing sulfone groups on the ketene portion and a methyl group on the imine portion of ketenimine *(141)*, the CH_3—N—C bond angle is 180°. Large contribution of resonance structure *(142)* can account for the linearity in the crystalline state. When the *N*-methyl group is replaced by an *N*-ethyl group, however, the CH_2—N—C bond angle is 144°.



(141a), R = Ph, R^1 = Ph

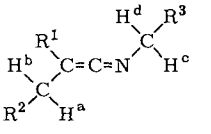
(141b), R = Ph, R^1 = CH_3

(142)

9.2. NMR Investigation of Stereochemistry

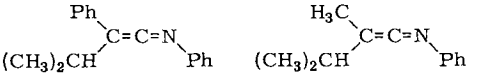
An attempt[52] to observe the effects of the barrier to interconversion of ketenimines on the chemical shift of diastereotopic methylene hydrogens in ketenimines *(143)* to *(146)*, shown in Table 11, was unsuccessful. The protons H^a, H^b or H^c, H^d appeared magnetically equivalent over a temperature range of −60 to +80 °C.

Table 11. Ketenimines used in an attempt to observe diastereotopic hydrogens [52].



	R^1	R^2	R^3
(143)	Ph	CH_3	*tert*-C_4H_9
(144)	Ph	Ph	*tert*-C_4H_9
(145)	Ph	CH_3	Ph
(146)	H	$C(CH_3)_2Cl$	*tert*-C_4H_9

Jochims and *Anet*[53] have used the NMR method to determine the barriers to racemization of *(147)* and *(148)*. At −113 °C the methyl protons of the isopropyl group of



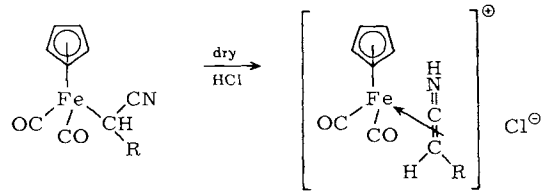
(147) *(148)*

(147) separate into a pair of doublets with a chemical shift difference of 4 Hz, corresponding to a free energy of activation for racemization of 9.1 ± 0.2 kcal/mole. The barrier in *(148)* is raised to 12.2 ± 0.3 kcal/mole.

10. Metal Complexes of Ketenimines

10.1. Metal π Complexes

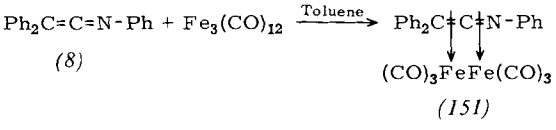
The ketenimine-iron π complex *(150)* was synthesized[54] by proton-catalyzed isomerization of σ complex *(149)*. The uncomplexed imine function can be identified by the characteristic infrared bands at 1554 cm^{-1}.



(149a), R = H
(149b), R = CH_3

(150a), R = H
(150b), R = CH_3

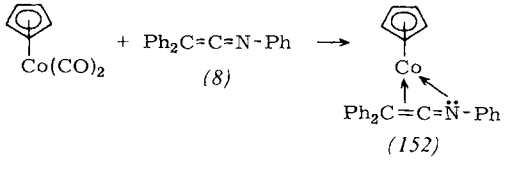
An iron complex *(151)* postulated[55] to be a di-π-complex is formed when triphenyl ketenimine *(8)* is heated with triiron dodecacarbonyl. In addition an unknown dimer of



(8) *(151)*

the ketenimine with CO inserted is formed. Diphenylketene-*N*-methylimine *(9)* forms a similar di-π-complex when reacted with $Fe_3(CO)_{12}$.

In contrast to the di-π-ketenimine-iron complex *(151)* is the σ-π-ketenimine-cobalt complex *(152)*. The cobalt complex is air-stable, can be chromatographed on alumina, and, unlike the free ketenimine *(8)*, is resistant to hydro-

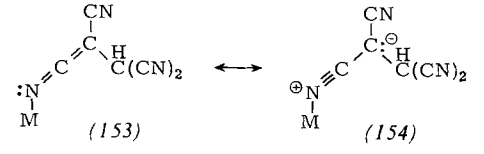


(8) *(152)*

lysis. The presence of the imine bond in uncomplexed form is inferred from infrared spectral evidence (band at 1565 cm^{-1}).

10.2. Keteniminato Transition Metal Complexes

A number of keteniminato transition metal complexes have been prepared[56] which contain a nitrogen-transition metal σ bond. X-ray studies have shown the structure of



(153) *(154)*

M = $-Ir(PPh_3)((CN)_2C{=}C(CN)_2)(CO)$

an iridium-tetracyanoethylene complex to be *(153)*[57]. An iridium-N—C bond angle of 162° is indicative of the relative importance of resonance structure *(154)*.

11. Chemical Behavior of Ketenimines

As the formal dehydration products of amides, ketenimines are readily converted into amide derivatives (Table 12). They add amines to form amidines *(155)*[58], water (catalyzed by acid) to form amides *(157)*, alcohols (catalyzed

Table 12. Some reactions of triphenylketenimine *(8)*.

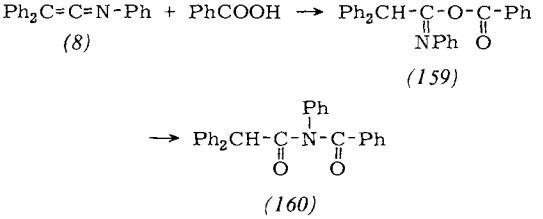
Reagent	Product	
$PhNH_2$	$Ph_2CH-C(=NPh)-NHPh$	*(155)*
H_2S	$Ph_2CH-C(=S)-NHPh$	*(156)*
H_2O/H^+	$Ph_2CH-C(=O)-NHPh$	*(157)*
CH_3OH/CH_3O^-	$Ph_2CH-C(=NPh)-OCH_3$	*(158)*
HCl	$Ph_2CH-C(=NPh)-Cl$	*(95)*
Cl_2	$Ph_2C(Cl)-C(Cl)=NPh$	*(94)*

by alkoxide) to form imidates *(158)*, and chlorine to form α-chloro imidoyl chlorides *(94)*[29]. Practical use has been made of ketenimines as dehydrating agents for a variety of purposes, as will be discussed in Section 11.1.

11.1. Ketenimines as Dehydrating Agents

11.1.1. Activation of Carboxyl Groups with Ketenimines

Triphenylketenimine dehydrates dicarboxylic acids, such as phthalic acid, to form anhydrides[59]; monocarboxylic acids react to form *N*-acyl amides *(160)*; which are rearrangement products of *O*-acyl imidic acids *(159)*. The intermediates *(159)* formed from *N*-protected amino acids can react with amino acid esters to form peptide bonds[60];



(8) *(159)* *(160)*

the active acylating agent *(159)* can be purified and stored, and the coupling reaction can be done in polar or nonpolar solvents. The reagent *(159)* can also be used to acylate alcohols.

Woodman and *Davidson*[61] found acetylketene-*N*-*tert*-butylimine *(161)* and acetic acid to result in a 95% yield

of the acetyl ester *(162)*. In order to prepare generally useful enol ester acylating agents, it is sufficient to start

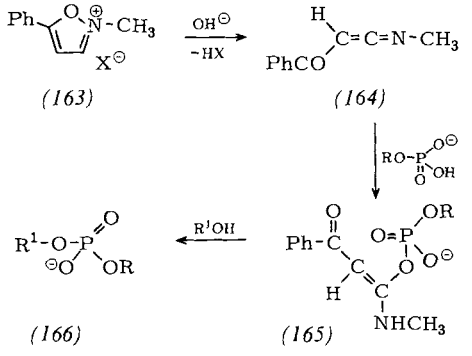
$$CH_3CO\text{-}CH{=}C{=}N\text{-}C(CH_3)_3 + CH_3COOH \longrightarrow$$
(161)

$$CH_3\text{-}\underset{\displaystyle O\text{-}CO\text{-}CH_3}{\overset{\displaystyle |}{C}}{=}CH\text{-}CO\text{-}NH\text{-}C(CH_3)_3$$
(162)

with the isoxazolium salt *(121)*. Compound *(121)*, $R^1=H$, $R^2=CH_3$, $R^3=C(CH_3)_3$ is the precursor of ketenimine *(161)* (see Table 9).

11.1.2. Preparation of Phosphorylating Agents

An excellent phosphorylating agent of the enolphosphate type is prepared from an isoxazolium salt *(163)* and phosphoric acid. Initial attack of base on the isoxazolium salt generates an acylketenimine *(164)* which is attacked by phosphoric acid monoester to form the active phosphorylating agent *(165)*. The reagent was used in the synthesis of nucleotide esters *(166)*, where R^1OH is a nucleotide, and the approach is presumably applicable to oligonucleotide synthesis[62].



(163) *(164)* *(166)* *(165)*

Some simple phosphates prepared from isoxazolium salts appear in Table 13.

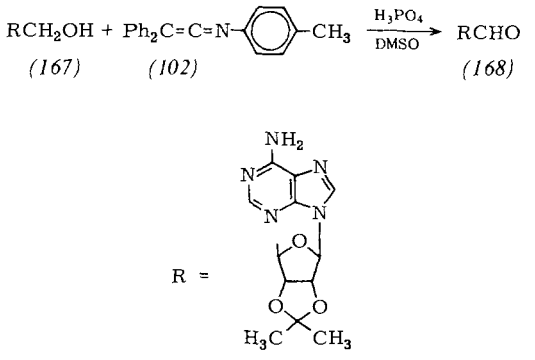
Table 13. Phosphates *(166)* prepared from isoxazolium salts [62].

$$R^1\text{-}O\text{-}\underset{\displaystyle {}^{\ominus}O}{\overset{\displaystyle O}{P}}{=}O \quad \underset{\displaystyle OR}{} \qquad (166)$$

R	R^1	Yield (%)
CH_3	Ph	89
C_2H_5	Ph	70
$(CH_3)_2CH$	Ph	73
$Ph{-}CH_2$	Ph	81

11.1.3. Oxidations Utilizing Ketenimines

Diphenylketene-*N*-*p*-tolylimine *(102)* has been used[63] in a novel oxidation of the 5'-hydroxyl group of an adenosine nucleoside *(167)*. The aldehyde *(168)* was obtained in 60% yield by the action of dimethyl sulfoxide and phosphoric acid on ketenimine *(102)*. This procedure has also been utilized in the oxidation of hydroxy steroids such as testosterone and cholesterol[64].

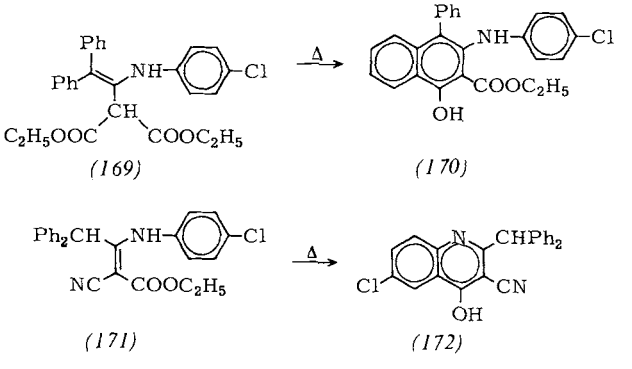


(167) *(102)* *(168)*

11.2. Additions of Carbanions and Grignard Reagents to Ketenimines

11.2.1. Reaction with Carbanions

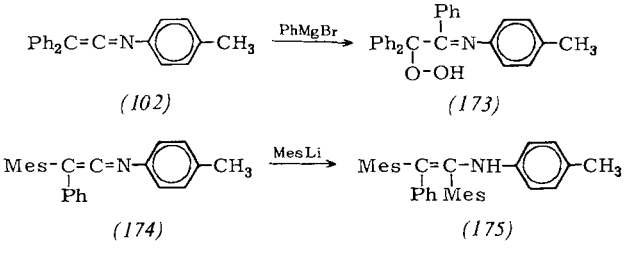
Diethyl malonate anion adds to triarylketenimines to give the α,β-unsaturated isomer *(169)* while ethyl cyanoacetate anion gives the α,β-unsaturated isomer *(171)*. Pyrolysis of these adducts yields the heterocycles *(170)* and *(172)* respectively[65].



(169) *(170)* *(171)* *(172)*

11.2.2. Reaction with Grignard Reagents

Stevens and *Gasser*[66] have isolated hydroperoxide *(173)* from the reaction of diphenylketene-*N*-*p*-tolylimine *(102)* with phenylmagnesium bromide. With the sterically hindered mesitylphenylketene-*N*-*p*-tolylimine *(174)* and mesityllithium only vinylamine *(175)* was isolated, however.

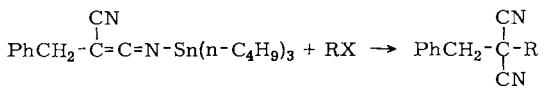


(102) *(173)* *(174)* *(175)*

11.3. Conversion of Ketenimines into Nitriles

11.3.1. Cleavage of the N—Sn Bond

N-Stannylketenimines react with a variety of reagents which cleave the nitrogen-tin bond to generate substituted malononitriles[15]. In Table 14 are shown the products *(176)* of cleavage of *N*-tri-*n*-butyl-stannylketenimine *(44)*

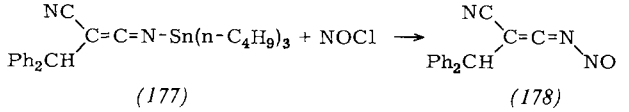


(44) (176)

Table 14. Cleavage products *(176)* of *N*-stannylketenimines *(44)*.

R	X	Yield (%)
H	C_2H_5O	68
$PhCH_2$	Br	85
CH_2=CH—CH_2	Br	94
$COOC_2H_5$	Cl	38
Ph_3C	Cl	67
Br	Br	90
PhCO	Cl	94

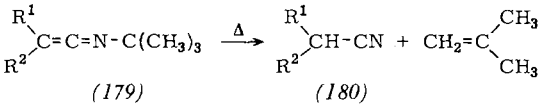
Preliminary studies[67] indicate that *N*-nitrosoketenimine *(178)* rather than the corresponding nitriles is formed when NOCl in tetrahydrofuran is used to cleave the tin-nitrogen bond of *(177)*.



(177) (178)

11.3.2. Pyrolytic and Photolytic Cleavage of Ketenimines

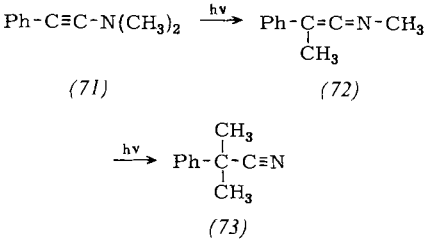
Several ketene-*N*-*tert*-butylimines *(179)* have been pyrolyzed at 145–160 °C in chloroform[68] to produce isobutylene and the nitriles *(180)*. *N*-Alkyl bond cleavage of ketenimine to nitrile has also been effected photolytically. Irradiation



(179) (180)

R^1 = Ph, R^2 = $COOCH_3$

R^1 = CF_3, R^2 = CF_3



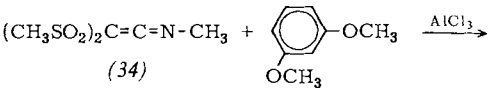
(71) (72)

(73)

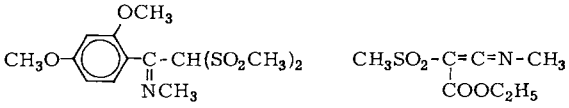
of ynamine *(71)* at 254 nm in cyclohexane[71] afforded trace amounts of dimethylbenzonitrile *(73)*, presumably *via* intermediate ketenimine *(72)*, identified by its infrared absorption.

11.4. Lewis-Acid-Catalyzed Aromatic Substitution with Ketenimines

Dijkstra and *Backer*[14a] found that ketenimine *(34)* undergoes an aluminum-chloride-catalyzed Friedel-Crafts reaction with resorcinol dimethyl ether in the absence of hydrochloric acid to give the imine *(181)*. Ketenimine *(36)* failed to undergo such an addition.



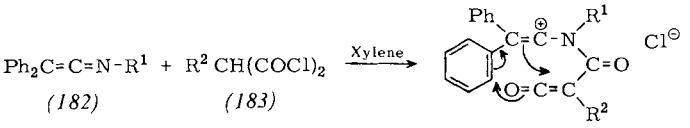
(34)



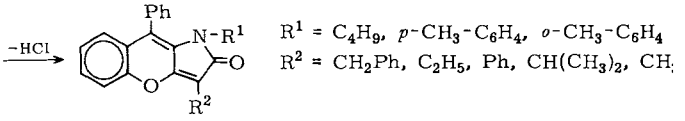
(181) (36)

11.5. Electrophilic Addition of Acid Chlorides to Ketenimines

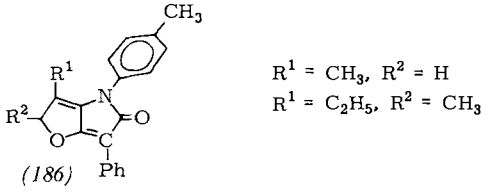
The structurally unusual heterocycles *(185)* have been synthesized[69] from ketenimines *(182)* and monosubstituted malonic acid chlorides *(183)* in refluxing xylene. Dimethyl- and diethylketene-*N*-*p*-tolylimines react with phenylmalonyl chloride to yield the heterocycles *(186)*.



(182) (183) (184)



(185)

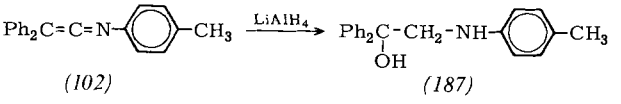


(186)

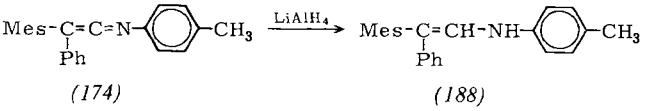
11.6. Reduction of Ketenimines

11.6.1. Hydride Reductions

Stevens and *Gasser*[66] found that amino alcohol *(187)* results from reduction of diphenylketene-*N*-*p*-tolylimine *(102)* with $LiAlH_4$. This reaction is assumed to proceed



(102) (187)

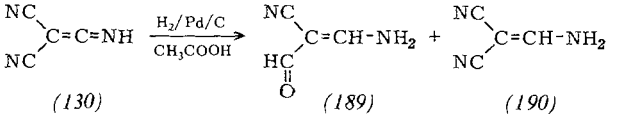


(174) (188)

through a hydroperoxide. The sterically hindered mesitylphenylketene-*N*-*p*-tolylimine *(174)* was reduced by $LiAlH_4$ to give a stable vinylamine *(188)*.

11.6.2. Catalytic Hydrogenation

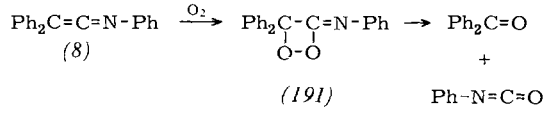
Catalytic reduction of cyanoform *(130)* yields compounds derived from the ketenimine tautomer[70]. 3-Amino-2-cyanoacrolein *(189)* and 3-amino-2-cyanoacrylonitrile *(190)* have been isolated as products.



(130) *(189)* *(190)*

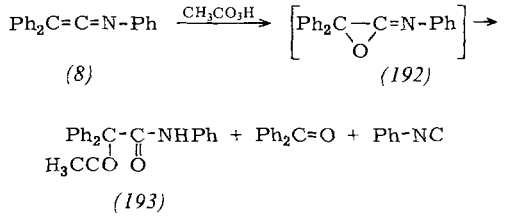
11.7. Oxidation Reactions of Ketenimines

Thermal cleavage of triphenylketenimine *(8)* with oxygen yields diphenyl ketone and phenyl isocyanate[1]. The products probably result from cleavage of an intermediate oxygen adduct *(191)*.



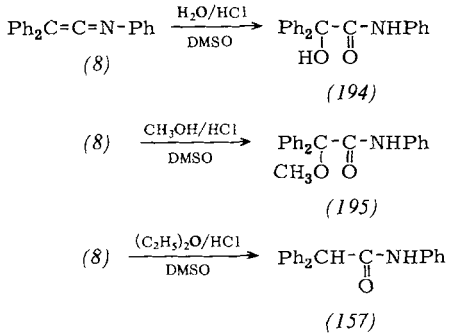
(8) *(191)*

Peracetic acid oxidation[71] cleaves triphenylketenimine *(8)* to form diphenyl ketone, phenyl isocyanide, and α-acetoxyamide *(193)*. The cleavage, presumably occurring *via* an α-imino epoxide *(192)*, is formally a reverse Passerini reaction.



(8) *(192)* *(193)*

The α-hydroxy amide *(194)* is formed from ketenimine *(8)* in 92% yield by the action of aqueous HCl in dimethyl sulfoxide. Use of methanolic HCl in dimethyl sulfoxide gave 70% yield of α-alkoxy amide *(195)*. When ether, dimethyl sulfoxide, and dry HCl were used, simple hydrolysis to amide *(157)* without oxidation of the ketenimine occurred during workup[72].



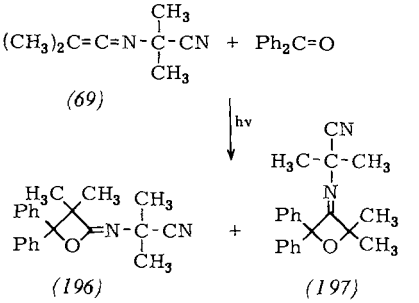
(8) *(194)* *(195)* *(157)*

11.8. Photochemical $[_\pi2_s+_\pi2_s]$ Cycloadditions of Ketenimines

Ketenimines should not differ markedly from alkyl-ethylenes in their capacity to function as $_\pi2_s$ components in cycloaddition reactions[73]. Indeed, a number of four-membered heterocycles have been synthesized by the photochemically allowed $[_\pi2_s+_\pi2_s]$ process. In certain cases described here this process may be stepwise but it is nevertheless expedient to consider the electrocyclic process in terms of allowed concertedness.

11.8.1. Cycloaddition of Carbonyl Compounds

Bartlett and *Singer*[74] observed photocycloaddition of aromatic aldehydes and ketones across the C=C double bond of dimethylketene-*N*-(2-cyanoisopropyl)imine *(69)* to give 2-iminooxetanes *(196)* and 3-iminooxetanes *(197)*. Those compounds that readily undergo photoadduct formation have an n—π* configuration for their lowest lying triplet state. Accordingly, 1-naphthaldehyde, with a lowest lying π—π* triplet state, failed to undergo photocyclization.



(69) *(196)* *(197)*

Table 15 shows a correlation of photoreactions of *(69)* with the energy required to convert an aromatic ketone from its ground state to its triplet state. The ketone also determines whether 2- or 3-iminooxetane is formed.

In a benzophenone-ketenimine reaction, cyclization proceeds *via* a triplet ketone reactive state[36]. In the case of fluorenone, however, adduct formation involves both singlet and triplet states[75].

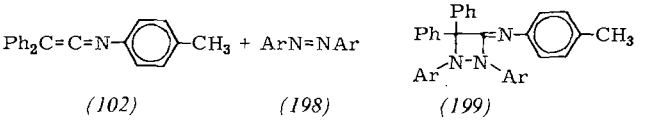
Table 15. Correlation of photoreactions of dimethyl-*N*-(2-cyanoisopropyl)ketenimine *(69)* with triplet energies of carbonyl compounds.

Carbonyl compound	E_{S-T} (kcal)	Adduct Yield (%)	Adduct Structure
cyclopropylphenyl ketone	—	0	—
acetophenone	74	43	2-imine + 3-imine
benzaldehyde	72	50	3-imine
benzophenone	70	95	2-imine + 3-imine
fluorenone	53	80	2-imine
1-naphthaldehyde	57 [a]	0	—

[a] Lowest lying triplet state results from a π—π* conversion.

11.8.2. Cycloadditions with Azobenzenes

Diphenylketene-*N*-*p*-tolylimine *(102)* adds under photolytic conditions[76] to various symmetrically substituted azobenzenes *(198)* to form diazetidinimines *(199)*. Some electron-donating substituents on the azobenzene system increase the rate of cyclization; however, electronic effects of substituents appear to be less important than the position of the substituent, as *o,o'*-dihydroxyazobenzene does not react.



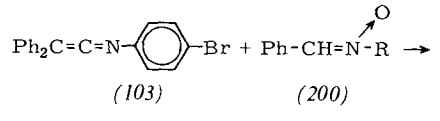
(102) *(198)* *(199)*

11.9. Thermal $[_\pi 4_s + _\pi 2_s]$ Cycloadditions

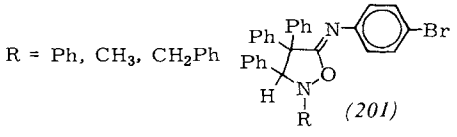
In the symmetry-allowed concerted $[_\pi 4_s + _\pi 2_s]$ reaction, ketenimines can serve as the $_\pi 2_s$ component either by utilizing the C=C or C=N linkages. Although triarylketenimines are not exceptionally reactive[77], several cycloadditions have been reported with ketenimines as $_\pi 2_s$ components in which the $_\pi 4_s$ component is a reactive 1,3 dipole.

11.9.1. Cycloaddition with Nitrones

Several 5-iminoisoxazolidines *(201)* have been synthesized[78] by the addition of nitrones *(200)* to diphenylketene-*N*-*p*-bromophenylimine *(103)*. An iminoisoxazolidine structure was assigned on the basis of known nitrone reactions and the manner in which nucleophiles add to ketenimines. Infrared absorption at 1680 cm^{-1} and mass spectral fragments at *m/e* 347 and 349 support the heterocyclic structure *(201)*.



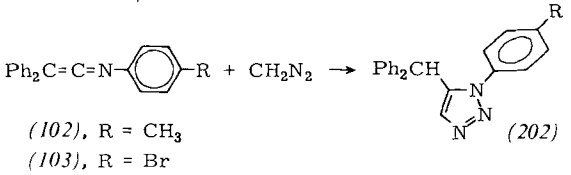
(103) *(200)*



(201)

11.9.2. Cycloaddition with Diazomethane

Triarylketenimines *(102)* and *(103)* reacted[79] with diazomethane by way of 1,3-addition to the imine function *(202)*. Other examples of cycloadditions to ketenimines have all involved the C=C double bond. 1,3 Cycloaddition did not occur, however, with diazoethane, phenyldiazomethane, and diphenyldiazomethane.

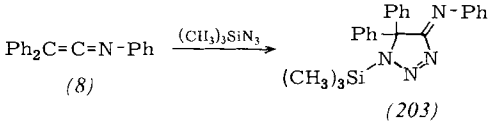


(102), R = CH_3
(103), R = Br

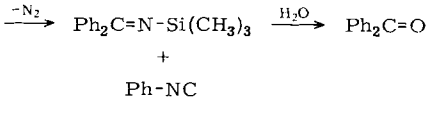
(202)

11.9.3. Cycloaddition with Trimethylsilyl Azide

Trimethylsilyl azide has been found to react with triphenylketenimine *(8)* on heating at 100 °C for 24 h[80]. Hydrolysis



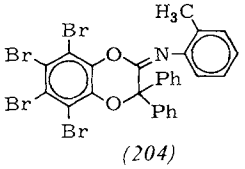
(8) *(203)*



of the reaction mixture afforded diphenyl ketones and phenyl isocyanate. The products presumably arise *via* decomposition of cycloadduct *(203)*.

11.9.4. Cycloadditions with *o*-Quinones

Diphenylketene-*N*-*o*-tolylimine reacts[81] with perhalogenated *o*-quinones to give quantitative yields of lactone anils *(204) via* a formal $[_\pi 4_s + _\pi 2_s]$ pathway.



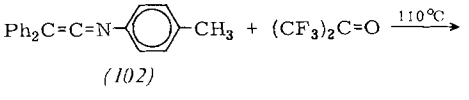
(204)

11.10. Thermal $[_\pi 2_s + _\pi 2_a]$ Cycloadditions

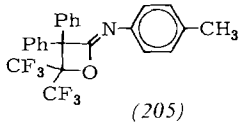
11.10.1. Ketones and Ketenimines

In principle ketenimines, functioning as vinylium ylides, are ideally constituted to play an antarafacial role as the $_\pi 2_a$ component in concerted thermal $[_\pi 2_s + _\pi 2_a]$ cycloadditions. This mode of addition, however, is not facile; attempted reactions of triphenylketenimine with phenyl isocyanate, sulfene, and phenylsulfene were unsuccessful[82].

It has been found[83], however, that diphenylketene-*N*-*p*-tolylimine *(102)* and bis(trifluoromethyl) ketone form a 2-iminooxetane adduct *(205)* when heated to 110 °C. If formed in a concerted process, the 2-iminoxetane may



(102)

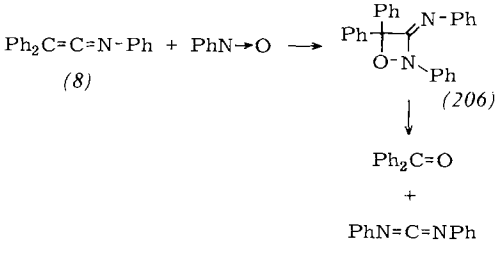


(205)

have arisen *via* a $[_\pi 2_s + _\pi 2_a]$ mode. No 3-iminooxetane was observed.

11.10.2. Nitroso Compounds and Ketenimines

Nitrosobenzene reacts with triphenylketenimine in refluxing chloroform to yield diphenyl ketone and diphenyl carbodiimide[84]. The presumed intermediate 3-iminooxazetidine *(206)* could be identified in solution by its 1705 cm^{-1} infrared band.

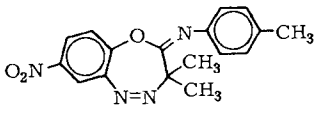


(8) *(206)*

11.11. Thermal $[_\pi 6 + _\pi 2]$ Cycloadditions

Halogen- or nitrosubstituted diazo-*o*-quinones react[85] with dimethylketene-*N*-*p*-tolylimine in inert solvents to form 2-imino-1,4,5-benzooxadiazepines *(207)*. Formation

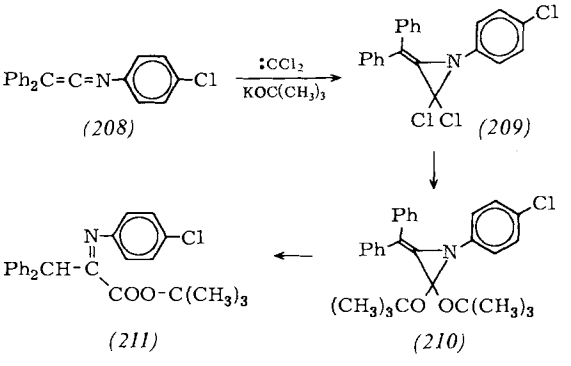
of *(207)* is formally a $[_\pi 6 + _\pi 2]$ cycloaddition in which one component must be used antarafacially for a concerted reaction.



(207)

11.12. Cheletropic Reactions

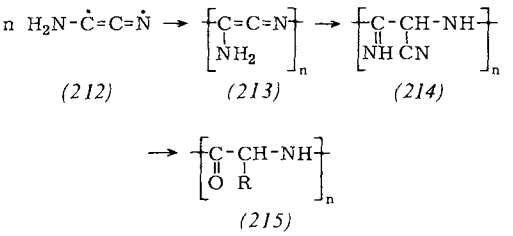
Ichimura and *Ohta*[86] have postulated the addition of dichlorocarbene to ketenimine *(208)* to form *(209)* in order to explain the formation of imine *(211)*. It is not known if dichlorocarbene adds to the C=C or C=N double bond, so this mechanism must be considered speculative.



(208) *(209)* *(211)* *(210)*

12. Ketenimines and Prebiological Protein Synthesis

Ketenimines have been implicated in chemical evolution studies to explain prebiological protein formation. *Kliss* and *Mathews*[87] have postulated that HCN formed by solar irradiation of a methane-ammonia atmosphere dimerized to yield the 1,3 biradical aminocyanomethylene *(212)*. Polymerization of this biradical results in formation of polyaminoketenimines *(213)*[88].



(212) *(213)* *(214)* *(215)*

Tautomerism of *(213)* followed by saturation with HCN forms a stereoregular helical polymer *(214)* which is eventually converted into polyglycine *(215)* (R = H) by hydrolysis and decarboxylation. The formation of polypeptides with side groups other than hydrogen occurs before hydrolysis by reaction of the nitrile groups of the polycyanide *(214)* with hydrogen cyanide, hydrogen sulfide, and acetylene, expected components of a primitive atmosphere. *Mathews* and *Moser*[89] have found in support of this proposal that HCN polymerization catalyzed by anhydrous ammonia followed by gradual hydrolysis results in the synthesis of polypeptides containing at least eight of the common α-amino acids.

It is likely that this polymerization sequence led to formation of a protein dominated layer which became concentrated in the oceans of primeval Earth and that this process is still occurring on Jupiter and other planets with atmospheres of methane and ammonia, the molecular precursors of HCN and life.

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[82] a) *G. Krow* and *J. McCormick*, unpublished observations; b) Ynamine-sulfene cycloadditions have been reported, however, by among others *M. Kuehne* and *P. Sheeran*, J. Org. Chem. *33*, 4406 (1968); *M. Rosen*, Tetrahedron Lett. *1969*, 647; c) For enamine-sulfene cycloadditions, see *G. Stork* and *I. Borowitz*, J. Amer. Chem. Soc. *84*, 313 (1962); *G. Opitz* and *H. Adolph*, Angew. Chem. *74*, 77 (1962); Angew. Chem. internat. Edit. *1*, 113 (1962); d) *G. Opitz*, Angew. Chem. *79*, 161 (1967); Angew. Chem. internat. Edit. *6*, 107 (1967), has reported the unsuccessful reaction of diphenylketene and sulfene.

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[84] *G. R. Krow* and *J. McCormick*, unpublished observation.

[85] *W. Ried* and *R. Junker*, Liebigs Ann. Chem. *696*, 101 (1966).

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[87] *R. M. Kliss* and *C. N. Mathews*, Proc. Natl. Acad. Sci. U. S. *48*, 1300 (1962).

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[89] *C. N. Mathews* and *R. E. Moser*, Proc. Natl. Acad. Sci. U. S. *56*, 1087 (1966).

Approaches to Total Synthesis of Heterocyclic Steroidal Systems[**]

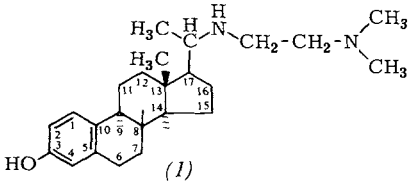
By H. O. Huisman[*]

In heterocyclic steroids the carbon atoms of the steroid skeleton (positions 1 to 17) are replaced in part by hetero atoms. The term generally denotes compounds containing one or two nitrogen, oxygen, and/or sulfur atoms. The part of the molecule containing the hetero atom is either introduced as a preformed unit or is constructed by stepwise synthesis. The examples given in the present article contain the hetero atoms in ring A, ring B, between rings A and B, and/or between rings C and D.

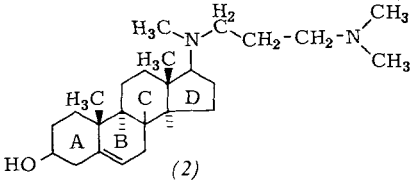
1. Introduction

Modified steroids have attracted a great deal of attention for several reasons: In the first place, their preparation itself is a stimulating challenge to the organic chemist, often demanding development of new and generally useful reactions; secondly, the investigations of reaction mechanism and stereochemistry, based upon the steroidal framework, provide fundamentally significant and frequently fascinating chemical problems; and thirdly, the biological properties of modified steroids have proved to be of interest.

A special class of modified steroids is represented by steroidal systems containing atoms other than carbon, usually nitrogen, oxygen, and sulfur, at various positions



(1)



(2)

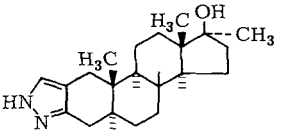
in the molecule. Such compounds have been prepared by partial or by total synthesis and some of them possess interesting pharmacological properties.

The two compounds *(1)*[1,2] and *(2)*[3-6] containing nitrogen atoms in the side chain of the steroid molecule serve as examples. These aza steroids exert a hypercholesterolemic activity[7-13].

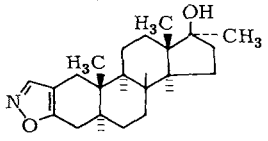
[*] Prof. Dr. H. O. Huisman
Laboratory of Organic Chemistry
University of Amsterdam
Amsterdam (The Netherlands)

[**] Lecture presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, July 7—11, 1969.

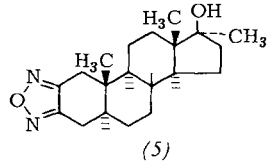
The four compounds *(3)*[14], *(4)*[15], *(5)*[16,17], and *(6)*[18] are representatives of heterocyclic steroids with high degree of separation of anabolic from androgenic activity. They contain a pyrazole-, isoxazole-, oxadiazole-, and a lactone ring respectively.



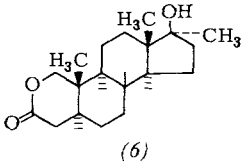
(3)



(4)

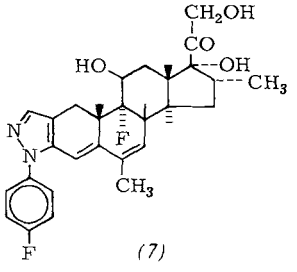


(5)



(6)

Pyrazole derivatives of 9-fluorocortisol systems, such as compound *(7)*[19], are heterocyclic steroids which possess potent anti-inflammatory activity.



(7)

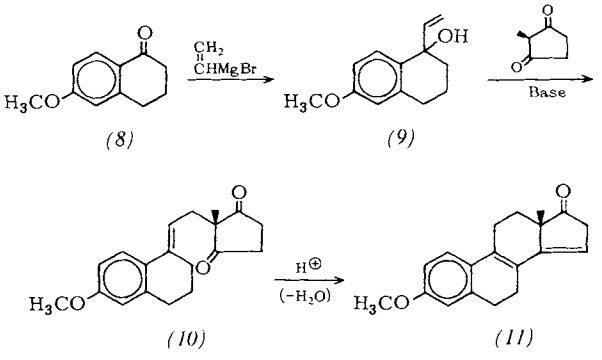
It may be noted that in all the examples mentioned—except compound *(6)*—the hetero atoms are located outside the steroidal nucleus. Thus only compound *(6)* can be termed a *heterocyclic* steroid. In our laboratory we have largely concentrated on the development of synthetic approaches leading to heterocyclic steroidal systems.

In principle, two different routes are available for the total synthesis of the complex steroid framework containing one or more hetero atoms. One approach starts from mono- or bicyclic hetero systems; alternatively, the heterocyclic component of the steroid nucleus may be constructed in a sequence of special synthetic techniques.

2. Utilization of Suitable Mono- or Bicyclic Hetero Systems to Construct the Heterocyclic Steroidal Skeleton

2.1. Approaches Based on *Torgov*'s Carbocyclic Steroid Synthesis

A synthetic scheme that holds considerable potentiality for variations in the nature of the precursor components is represented by the transformation of 6-methoxy-α-tetralone *(8)* to the steroidal skeleton *(11)* in three facile

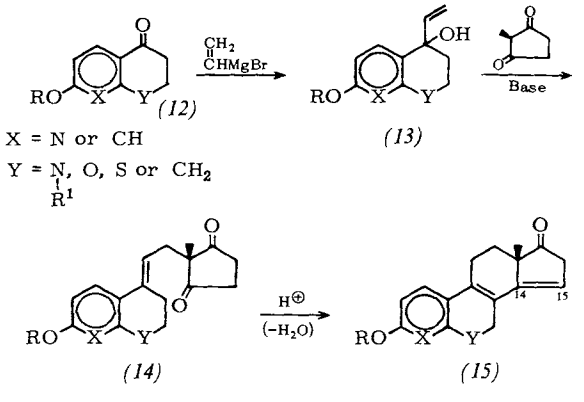


(8) *(9)* *(10)* *(11)*

steps in good overall yields. This elegant total synthesis was developed by *Torgov et al.*[20] at Moscow.

It is obvious that α-tetralone should be replaceable by various heterocyclic analogs, provided the nature and location of the hetero atom(s) do not adversely affect the sequence of reactions involved.

Using appropriate aza-, oxa-, and thia-α-tetralones *(12)*, tetracyclic systems *(15)* have been prepared according to Scheme 1.



(12) *(13)* *(14)* *(15)*

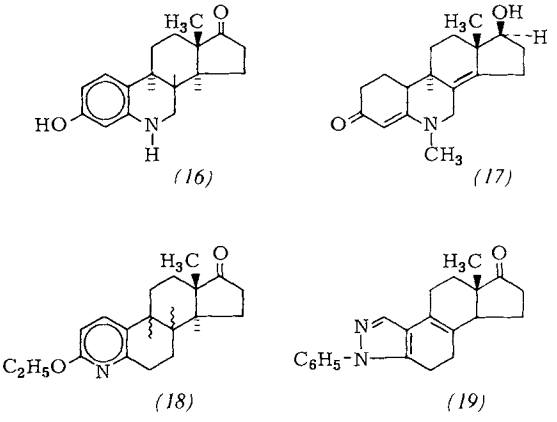
X = N or CH

Y = N, O, S or CH_2 (R^1)

Scheme 1.

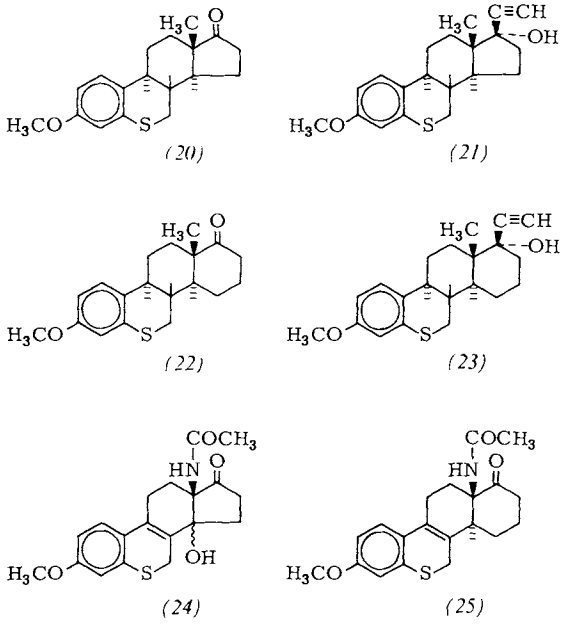
Neither the mechanism of the condensation reaction by which the *seco*-diones *(14)* are formed, nor the mechanism of the cyclodehydration reaction which leads to the tetracyclic systems *(15)* will be discussed here. Nor will details of how the tetracyclic systems *(15)* have been further elaborated to various aza, oxa, and thia steroids be given. Most of this work has been extensively reviewed elsewhere[21].

However, in order to emphasize the versatility of this three-step synthesis, the various heterocyclic steroidal systems synthesized by this method are summarized in Table 1.



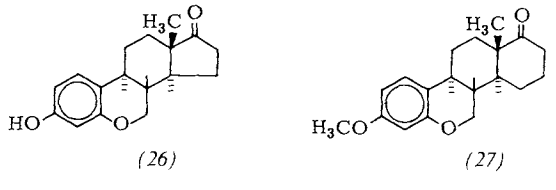
(16) *(17)* *(18)* *(19)*

The D-homo thia steroidal systems *(22)* and *(23)* have been obtained by using methylcyclohexadione instead of methylcyclopentadione in the condensation reaction. The thia steroidal systems *(24)* and *(25)*, which both contain an acetylamino group in place of an axial methyl group at



(20) *(21)* *(22)* *(23)* *(24)* *(25)*

position 13, have been synthesized by using acetylaminocyclopentadione and acetylaminocyclohexadione respectively in the condensation reactions.



(26) *(27)*

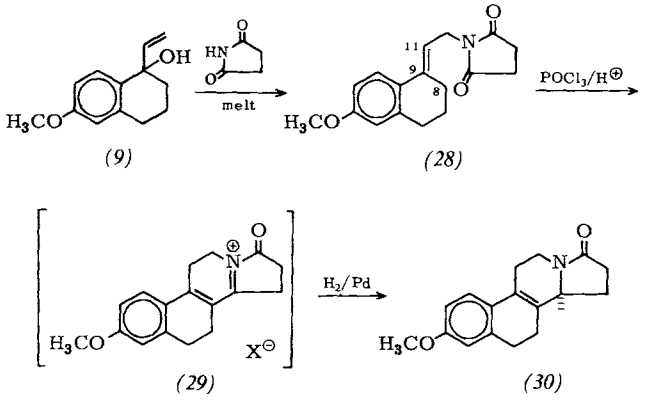
Recently we have utilized heteroanalogs of the cyclopentadione systems in the above reaction scheme for the synthesis of ring D-modified steroids. From a consideration of the mechanism of the addition and cyclization steps, it is apparent that the choice of a dione analog is subject to several structural restrictions. In view of its weak acidic character and cyclic lactam structure the candidate selected was the readily available succinimide system. Furthermore, the chemical properties of the latter system necessitated

Table 1. Heterocyclic steroids synthesized by *Torgov*'s method.

Compound		Ref.
Aza steroids		
(16)	(±)-6-azaestrone	[22—28]
(17)	(±)-17β-hydroxy-6-methyl-6-azaestra-4,8(14)-dien-3-one [(±)-*N*-methyl-6-aza-8,14-di-dehydro-19-nortestosterone]	[29—32]
(18)	(±)-3-ethoxy-4-azaestra-1,3,5(10)-trien-17-one [(±)-4-azaestrone ethyl ether]	[33, 34]
(19)	(±)-A-nor-3-phenyl-2,3-diazaestra-1,5(10),8,14-tetraen-17-one	[35]
Thia steroids		
(20)	(±)-3-methoxy-6-thiaestra-1,3,5(10)-trien-17-one [(±)-6-thiaestrone methyl ether]	[36, 37]
(21)	(±)-17β-ethynyl-3-methoxy-6-thiaestra-1,3,5(10)-trien-17α-ol [(±)-17-ethynyl-6-thia-estradiol 3-methyl ether]	[37]
(22)	(±)-3-methoxy-6-thia-D-homoestra-1,3,5(10)-trien-17-one [(±)-6-thia-D-homoestrone methyl ether]	[38]
(23)	(±)-17β-ethynyl-3-methoxy-6-thia-D-homo-estra-1,3,5(10)-trien-17α-ol [(±)-17-ethynyl-6-thia-D-homoestradiol 3-methyl ether]	[38]
(24)	(±)-18-acetyl-14ξ-hydroxy-3-methoxy-6-thia-18-azaestra-1,3,5(10),8-tetraen-17-one [(±)-8,9-didehydro-13-acetylamino-14-hydroxy-6-thia-18-norestrone methyl ether]	[39]
(25)	(±)-18-acetyl-3-methoxy-6-thia-18-aza-D-homoestra-1,3,5(10),8-tetraen-17-one [(±)-8,9-didehydro-13-acetylamino-6-thia-18-nor-D-homoestrone methyl ether]	[39]
Oxa steroids		
(26)	(±)-6-oxaestrone	
(27)	(±)-3-methoxy-6-oxa-D-homoestra-1,3,5(10)-trien-17-one [(±)-6-oxa-D-homoestrone methyl ether]	[40, 41]

modification of the usual reaction conditions. A generally applicable new technique for this type of condensation was found by carrying out the reaction in a melt in presence of a base, usually potassium succinimide. In this way slow reaction of the succinimide at low temperatures and instability of the vinyl alcohol *(9)* at high temperature could be overcome.

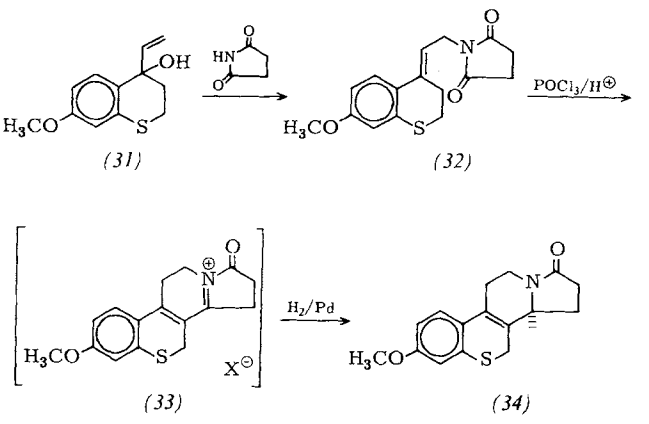
The sequence of reactions is given in Scheme 2. Cyclodehydration of the *seco*-steroid *(28)* was carried out by treatment with a mixture of phosphorus oxychloride and water, in which the latter served as a proton source for acid-catalyzed isomerization of the 9,11 double bond to the 8,9 position prior to the cyclization step. The unstable cyclization product *(29)* was directly hydrogenated to the 13-aza-steroidal system *(30)*[42,43].



(9) *(28)* *(29)* *(30)*

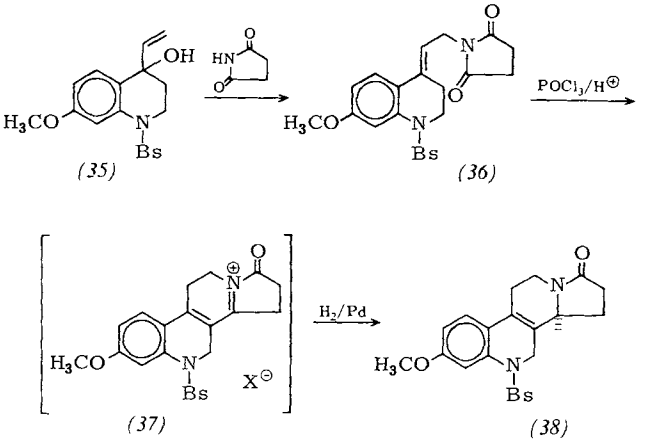
Scheme 2.

Reaction of succinimide with vinyl alcohols derived from heterocyclic analogs of 6-methoxy-α-tetralone should, in principle, lead to heterocyclic steroidal systems containing an assortment of combinations of elements. An example illustrating the application of Scheme 2 to this class of compounds may be seen in the synthesis of the 6-thia-13-aza-steroidal system *(34)* starting with the vinyl thia alcohol *(31)*[43,44].



(31) *(32)* *(33)* *(34)*

Another example is the synthesis of the 6,13-diaza-steroidal system *(38)*[43,45] starting with the vinyl aza alcohol *(35)*.

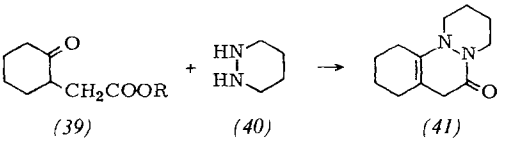


(35) *(36)* *(37)* *(38)*

Bs = C_6H_5-SO_2-

2.2. Approaches by Condensation Reactions with Hydropyridazines

A second general approach using accessible heterocyclic precursors, and one which is potentially open to ample variations, is embodied in the reaction of perhydropyridazine *(40)* with an alkyl (2-oxocyclohexyl)acetate *(39)*.

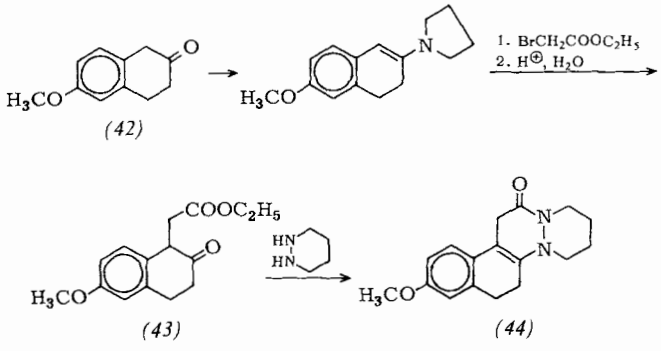


(39) *(40)* *(41)*

The direct condensation yields a tricyclic system *(41)*[46,47] containing vicinal nitrogen atoms at a bridgehead location. The reaction actually proceeds in two consecutive steps; initial amide formation is followed by a fast intramolecular cyclization[*].

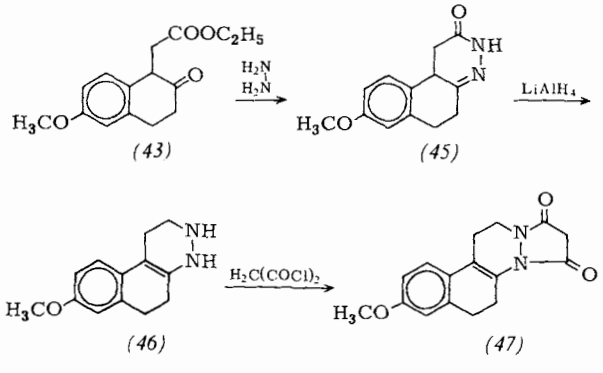
Depending upon the availability of the appropriate γ-keto esters *(39)* it is easy to visualize that the reaction sequence offers an attractive approach to 5,10- or 13,14-diaza-steroidal systems. Both these objectives have been achieved in our laboratory.

The starting point for a 13,14-diaza-steroidal skeleton was 6-methoxy-β-tetralone *(42)* which was conveniently monoalkylated with ethyl bromoacetate at the α-position, *via* its pyrrolidine enamine to the γ-keto ester *(43)*. Reaction of the latter with perhydropyridazine in boiling xylene afforded the 13,14-diaza-D-homo-steroidal system *(44)*[48].



(42) *(43)* *(44)*

A slight modification of the hydrazine condensation principle may be seen in the synthesis of the 13,14-diaza-15,17-dioxo steroid *(47)*[48], where the tricyclic hydrazine *(46)* is itself prepared by the reaction of *(43)* with hydrazine hydrate, followed by reduction of *(45)*. The structure of *(47)* was evidenced by its IR, NMR and mass spectral (exact mass) data.

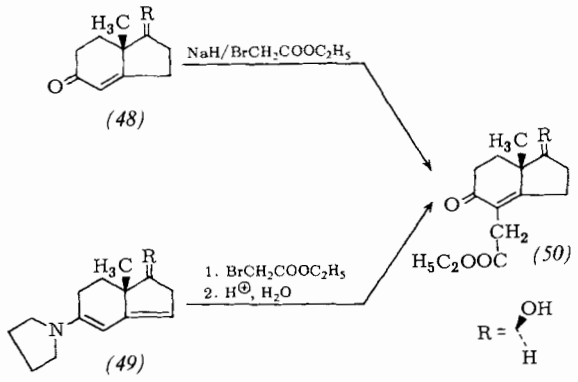


(43) *(45)* *(46)* *(47)*

In order to introduce the vicinal nitrogen atom between rings A and B of the steroidal nucleus (Positions 5 and 10), it is necessary to operate with a functionalized tetrahydropyridazine and a γ-keto ester component incorporating preformed rings C and D.

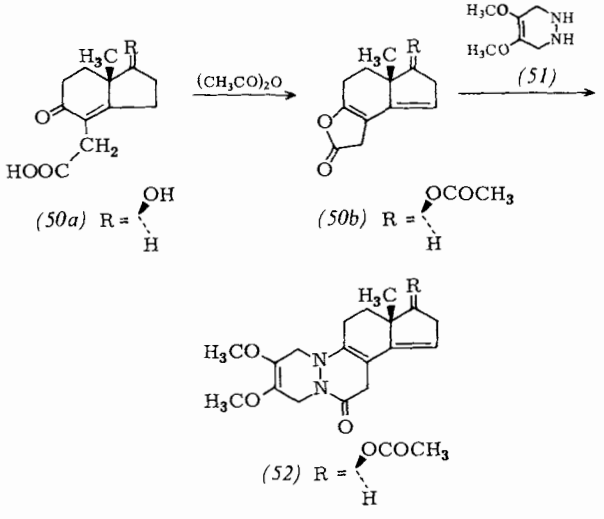
The intermediate *(50)* was obtained by alkylation of the bicyclic ketone *(48)*, in presence of base or, preferably, *via* the enamine *(49)*.

[*] The two-step sequence has been substantiated by isolation of the intermediate amide, which undergoes rapid cyclization.



(48) *(49)* *(50)*

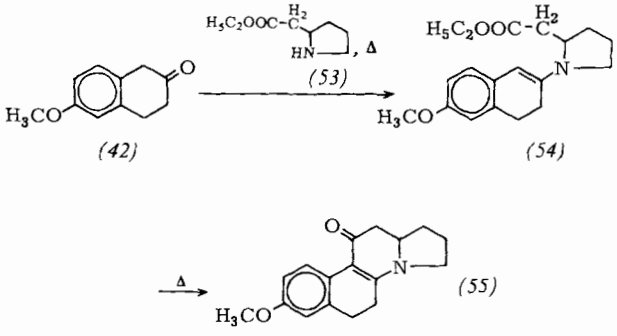
By heating the γ-keto acid *(50a)* with acetic acid anhydride, the lactone *(50b)* is formed, which upon condensation with 4,5-dimethoxy-1,2,3,6-tetrahydropyridazine *(51)* affords the 5,10-diaza-steroidal system *(52)*[49,50].



2.3. Approaches by Intramolecular Cyclizations of Enamine Esters

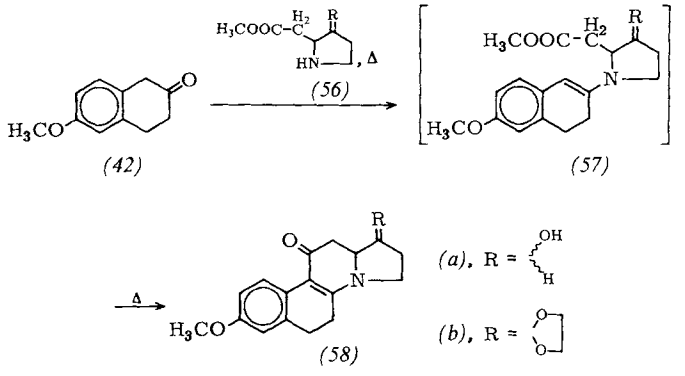
A third approach for building up aza-steroidal systems, especially the 14-aza-steroid skeleton, proceeds by intramolecular cyclization of enamine esters derived from β-tetralone and appropriately substituted pyrrolidines.

The principle of the reaction is illustrated by the condensation cyclization sequence upon heating a mixture of 6-methoxy-β-tetralone *(42)* and pyrrolidyl-2-acetate *(53)*. The intermediate enamine ester *(54)* is readily cyclized to the 11-keto-14-aza-steroidal system *(55)*[51] upon heating in glycol.



(42) *(54)* *(55)*

Substitution at C-17 in the steroidal system leading to 11-oxo 14-aza steroids *(58a)* and *(58b)* was achieved by reaction of the β-tetralone system with 3-substituted pyrrolidine esters *(56a)* and *(56b)*.

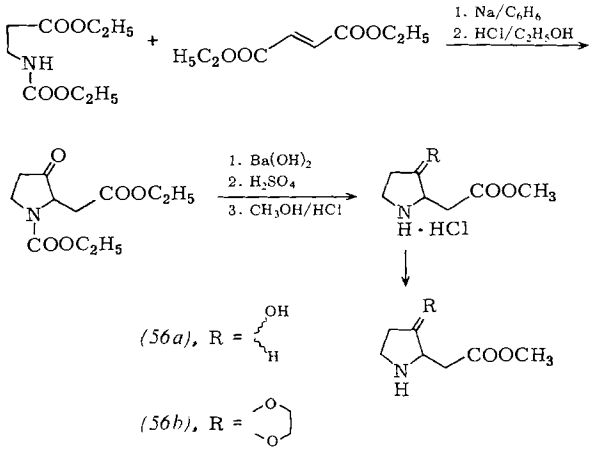


(42) *(57)* *(58)*

(a), R =

(b), R =

The 3-substituted pyrrolidine esters[52] are synthesized as shown in Scheme 3.

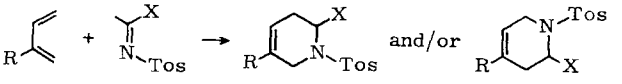


(56a), R =

(56b), R =

Scheme 3.

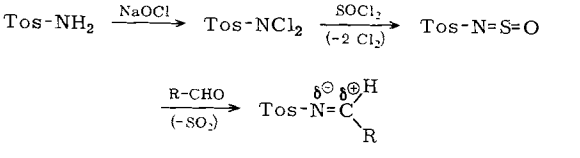
structural parameters satisfy certain requirements. For instance, electron-demanding groups such as trihalomethyl,



Scheme 4. X = CCl_3, $COOR^1$.

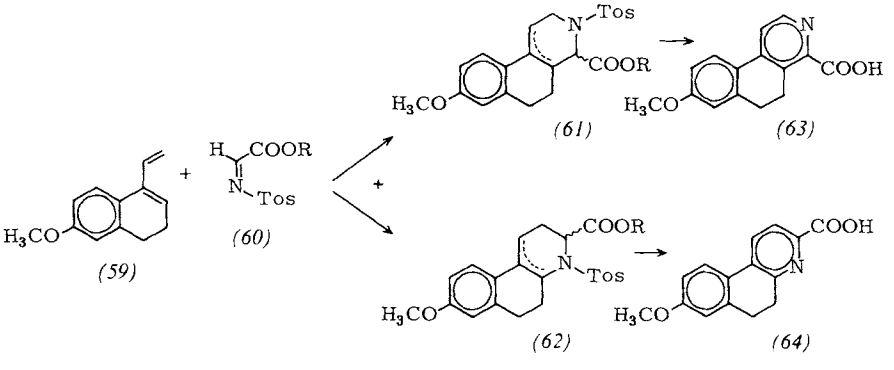
alkoxycarbonyl, or sulfonyl activate an imine sufficiently for it to act as dienophile in Diels-Alder reactions.

The practical difficulties connected with the synthesis of such highly reactive imines could be solved by using an adapted method for their preparation, which made it possible to carry out large scale preparations (Scheme 5).



Scheme 5. R = CCl_3, $COOR^1$.

A knowledge of the electronic and steric factors[*] which govern the direction of addition is of special interest in this type of Diels-Alder reaction. We have carried out a large number of investigations in order to gain fundamental information about the reactivity of diene systems and the direction of addition of the different imines to the dienes. However, this article will consider only those aspects which are of immediate importance in the synthesis of aza steroids.



(59) *(60)* *(61)* *(62)* *(63)* *(64)*

3. Construction of the Heterocyclic Component of the Steroid Nucleus in a Critical Synthetic Sequence

3.1. Preparation by Diels-Alder Cyclization

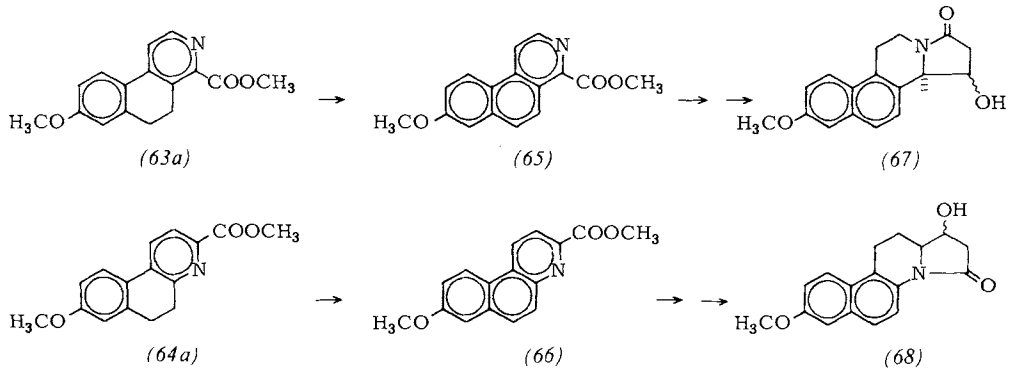
Use of Diels-Alder cyclization to form heterocyclic systems provides a general synthetic concept with a wide range of potential applications in steroid synthesis. Our own specific interests centered upon the reaction of suitable dienes with imines (Scheme 4).

Imines are generally recognized as being unreactive in cycloaddition reactions. However, some pioneering work of *Kresze* and collaborators[53] has indicated the possibility of a concerted type of addition of imines, provided that the

By reacting the imino ester *(60)* with the diene *(59)*, a laboriously separable mixture of isomeric adducts *(61)* and *(62)* is obtained, which, however, after alkaline hydrolysis yields the dihydrobenzoquinoline acids *(63)* and *(64)* (readily separated *via* fractional crystallization).

The corresponding methyl esters of these acids, *(63a)* and *(64a)* respectively, were dehydrogenated to the benzoquinolines *(65)* and *(66)*, which where converted *via* standard procedures to the 13-aza- and 14-aza-equilenine systems *(67)* and *(68)*[55, 56].

[*] General information about these factors was obtained from a series of experiments wherein the mode of addition of simple dienes was studied. Results will be published separately [54].

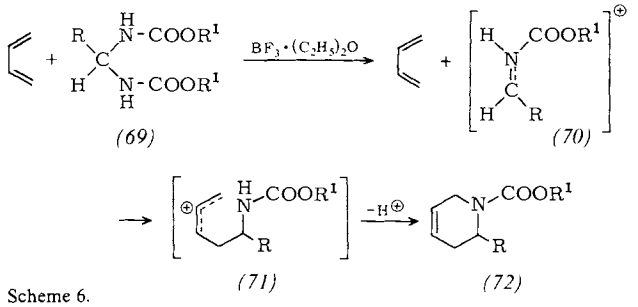


(63a) (65) (67)

(64a) (66) (68)

3.2. Preparation by a Pseudo Diels-Alder Reaction (Urethane Approach)

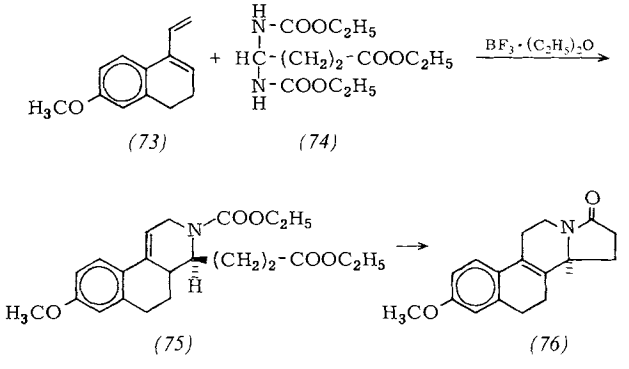
A second approach is based on a reaction type that formally resembles a normal Diels-Alder cycloaddition between an imine and a diene, but is mechanistically of a different class[57]. One could call it a pseudo Diels-Alder reaction; it proceeds as shown in Scheme 6.



(69) (70) (71) (72)

Scheme 6.

Under the influence of BF_3·ether, a diene reacts with a dicarbamate *(69)* to give a tetrahydropyridine derivative *(72)*. The type of reaction involved in this addition is most probably the following: After the generation of a carbonium ion intermediate *(70)* an addition complex *(71)* is formed which then cyclizes to give the heterocyclic system

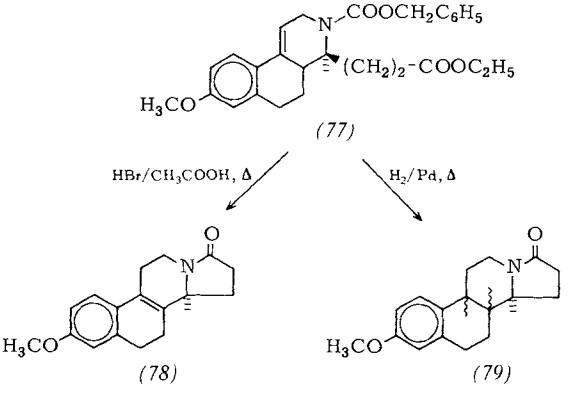


(73) (74) (75) (76)

(72). Promoting factors in this condensation are, among others, the stability of the ion *(70)*, the presence of stabilizing groups R, and especially the rigidity of the diene. The last factor obviously reflects a favorable entropy factor necessary for a smooth cyclization of the ionic intermediate. Experimental evidence for this observation comes from a large series of reactions with a variety of diene systems[58].

The original synthetic scheme developed made use of a particular advantage of this method in which the choice available in the substituent R could be exploited by choosing a group which potentially includes the factors of ring D in the steroid molecule. The diene *(73)* reacts with the dicarbamate *(74)* to give the tricyclic intermediate *(75)* which after hydrolysis of the ester groupings cyclizes to the 13-aza steroid *(76)*. However, the yield in the last step, the cyclization reaction, was rather low.

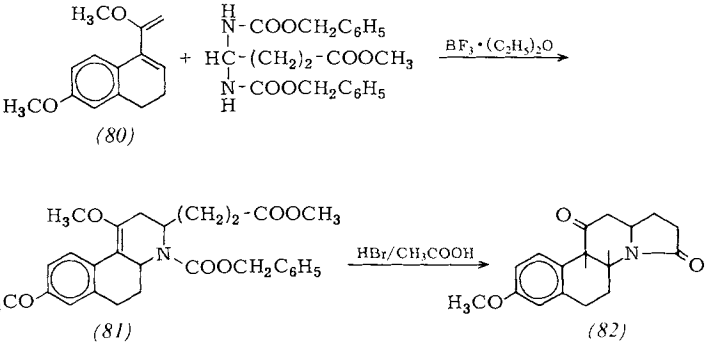
A considerable improvement in the yield of the cyclization step was achieved on use of the benzylurethane moiety instead of the ethylurethane group in *(75)*. The crystalline adduct *(77)* was obtained *via* the indicated route and



(77) (78) (79)

smoothly converted into the aza steroids *(78)* and *(79)* by treatment with hydrobromic acid/acetic acid and hydrogenation over palladium on carbon[59], respectively.

The method outlined was further applied to the synthesis of 11-oxo 14-aza steroids using diene *(80)* as starting material. In view of the polarization of the diene system one should expect predominant formation of the 14-aza

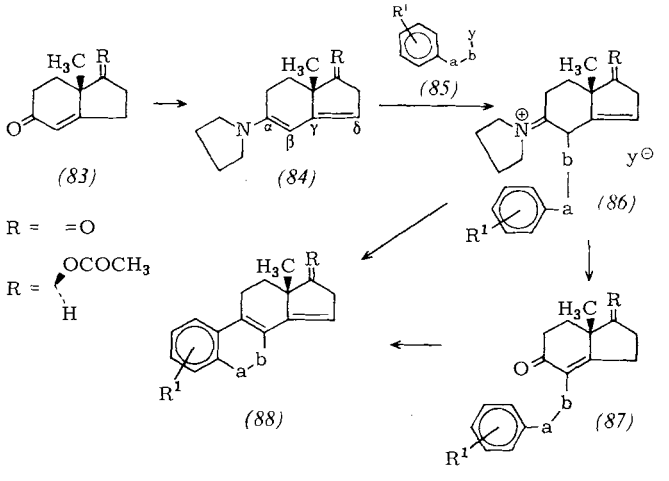


(80) (81) (82)

isomer *(81)*, which was actually observed. Acid-catalyzed cleavage of the benzyloxycarbonyl group led to the 14-aza-steroidal system *(82)*[60].

3.3. Preparation by Condensations of Suitable Dienamine Systems

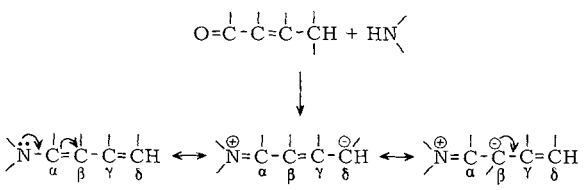
The principle of the method may be outlined as follows: A dienamine *(84)* of the readily accessible bicyclic α,β-unsaturated ketone *(83)*—which eventually serves as the C/D portion of the steroid nucleus—is connected, *via* the β-carbon, to an appropriate functionalized aromatic derivative, such as *(85)*. Hydrolysis of the intermediate iminium salt *(86)* unmasks the carbonyl function, which then serves as the point of cyclization of the aromatic ring; the overall process results in the formation of the steroidal skeleton *(88)*. It is conjectured that the intermediate *(86)* can also directly undergo a cyclization reaction involving nucleophilic attack.



For the scheme to operate several essential requirements must be satisfied: a) electrophilic attack on the enamine must occur on the β-position (and not on the δ); b) Y should be a good leaving group; and c) the aromatic ring should be sufficiently activated so as to undergo electrophilic attack by the carbonyl carbon under the influence of suitable acidic reagents.

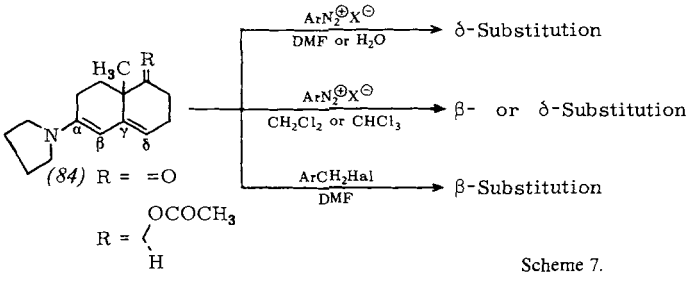
A dienamine system has, in principle, three nucleophilic centers—the nitrogen atom, and the β- and δ-carbon atoms. The latter derive their nucleophilic character by interaction of the free electron pair of the nitrogen with the π-electrons of the double bond.

A comparison of dienamines with dienol ethers[61] and a consideration of the value of the chemical shift of the olefinic protons of cyclic dienamines both suggest a charge distribution in the dienamine where the β-carbon has a



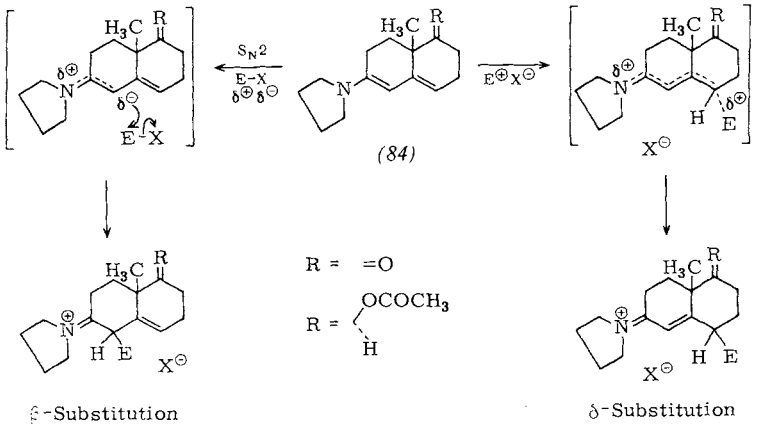
higher electron density than the δ-carbon. This charge distribution has been substantiated by HMO calculations[62] of the electron-density along the dienamine system: α-C = +0.0754; β-C = −0.1258; γ-C = +0.0080; δ-C = −0.0629.

An interesting insight into the electrophilic pattern of dienamines is afforded by the reaction of systems such as *(84)* with reagents of different reactivities and under varying reaction conditions (see Scheme 7).



Scheme 7.

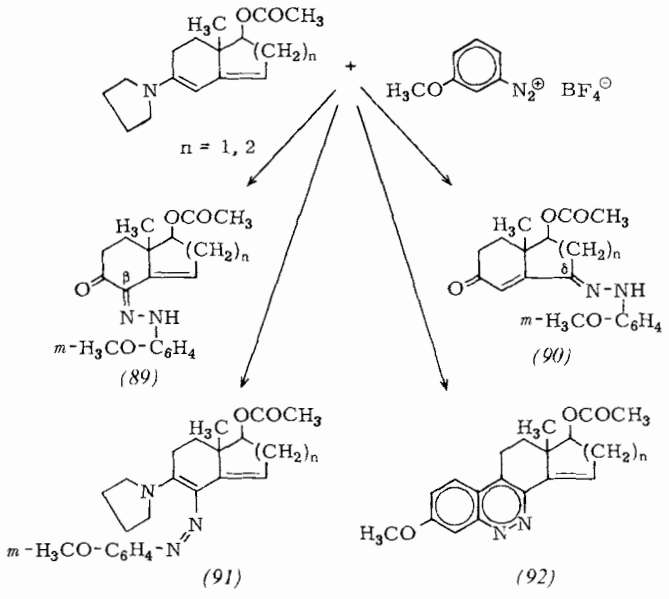
The following rationalization may be offered for the substitution pattern of the dienamine system. β-Substitution results from nucleophilic attack (S_N2) by the atom with the higher charge density and involves bond cleavage in the transition state[*]. With a charged electrophile, such



Scheme 8.

[*] We have so far no evidence for an initial attack on the nitrogen followed by an N→C migration. However, this and related questions concerning the mechanism are presently being investigated.

as a diazonium salt in polar solvents, the transition state—essentially a "clipping-on" process—closely resembles the

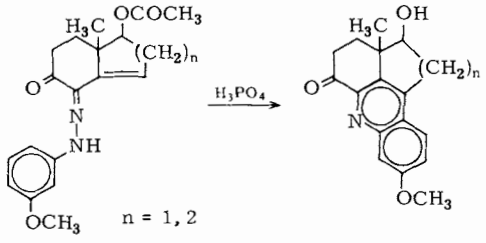


end product and its structure may consequently be dominated by the thermodynamic stability of the product. This results in the formation of the conjugated iminium salt, *i.e.* the product of δ-substitution[*]. In methylene chloride or chloroform, however, reaction of diazonium salts may proceed *via* the simultaneous operation of both mechanisms (Scheme 8).

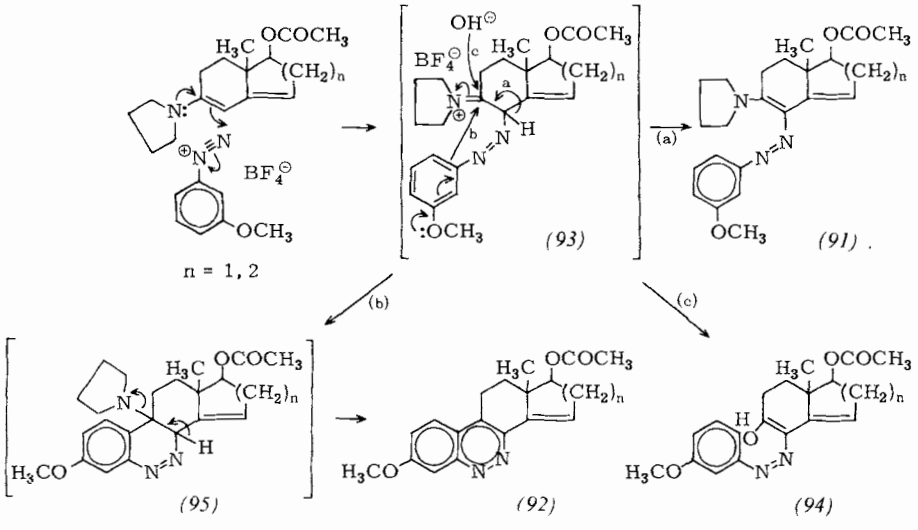
[*] We are aware that alternative explanations can be offered for δ-substitution. A study of the influence of solvent effects of substituents in the diazonium salts is being conducted at present to settle the issue.

The products of the diazonium salt reaction with the dienamine in CH_2Cl_2 or $CHCl_3$ have been identified as the expected β-hydrazone *(89)* and δ-hydrazone *(90)* and, what was of greater interest, the azoenamine *(91)* and the 6,7-diaza-steroidal system *(92)*[63].

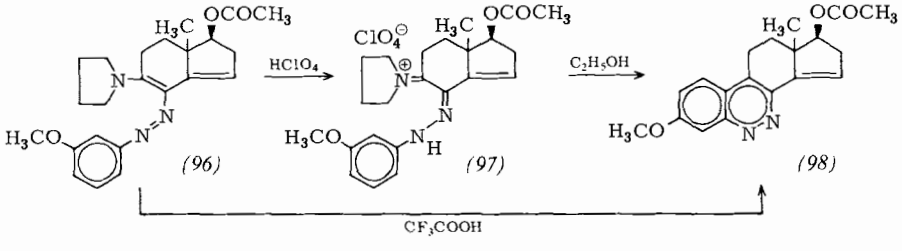
The origin of the β-substitution products can be seen in the different fates of the initially formed iminium ion *(93)*. Loss of a proton (path a) leads to the azo enamine *(91)* while hydrolysis (path c) gives the hydrazone *(94)* depicted in its tautomeric form [cf. *(89)*]. Formation of the steroidal system *(92)* can be explained by an intramolecular nucleophilic attack by the aryl moiety on the iminium function



(path b), followed by loss of pyrrolidine from the intermediate product *(95)*.



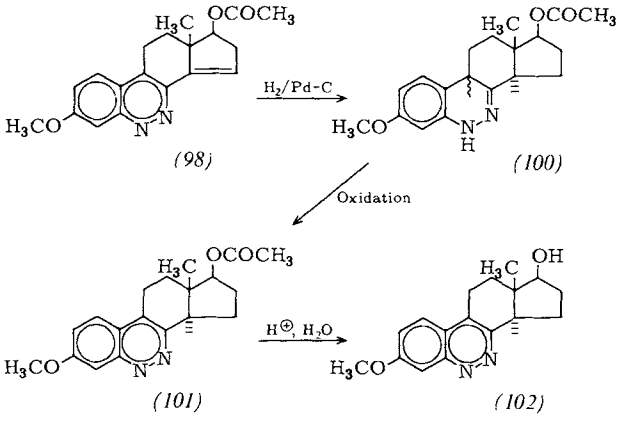
That this indeed was the course of events is supported by the fact that both heating of the azo enamine *(96)* [cf. *(91)*] in trifluoroacetic acid and refluxing the iminium perchlorate *(97)* in ethanol resulted in the formation of the steroidal system *(98)* [cf. *(92)*] in high yield.



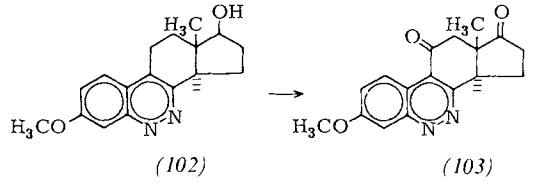
Attempts to cyclize the β-substituted hydrazone *(89)* to the steroidal skeleton were unsuccessful. Instead, under

acidic conditions, cyclization led to the quinoline derivative *(99)*.

Elaboration of the steroidal system *(98)* to the 6,7-diaza analogs of estrogenic hormones was then undertaken.

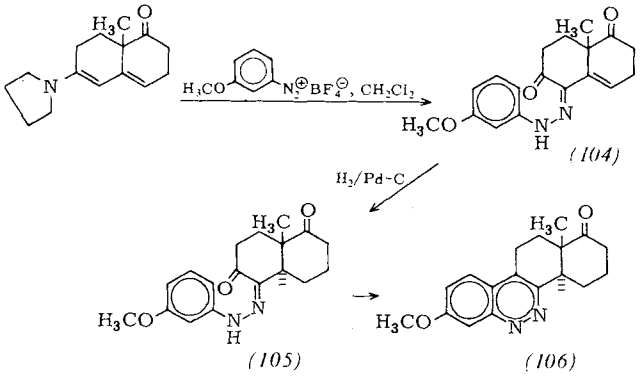


Catalytic reduction over Pd—C effects partial hydrogenation of the heterocyclic ring, and complete reduction of the 14,15-double bond. Only a single product *(100)* is isolated in which, while the stereochemistry of the proton on C-9 remains unsettled, the configuration of that on C-14 is shown to be α- by oxidation to *(101)*, whose NMR spectrum reveals *trans* C/D ring linkage. Acidic hydrolysis of *(101)* gives the corresponding alcohol *(102)*.

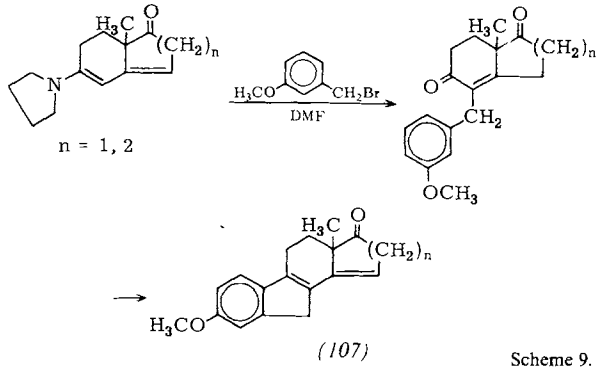


Attempts to convert *(102)* into 6,7-diazaequilenin methyl ether by oxidation with CrO_3/pyridine gave, interestingly, the 11-oxo derivative *(103)* of the desired compound. The relative ease of oxidation of the 11-position has also been observed with other oxidizing agents. Methods of specific oxidation of the OH group on C-17 are at present under investigation.

In view of the problems associated with the selective oxidation of the hydroxyl function on C-17 an approach starting from the β-hydrazone *(104)* was developed. Catalytic reduction of the β-substituted hydrazone resulted in a single product *(105)* which gave 3-methoxy-6,7-diazo-D-



homoequilenin *(106)* (3-methoxy-D-homo-6,7-diazaestra-1,3,5(10),6,8-pentaen-17-one) on treatment with polyphosphoric acid. The stereochemistry of the proton on C-14 in *(105)* and in *(106)* has been established by a comparison of the NMR spectrum of *(106)* with those of the carbocyclic D-homoequilenin and D-homo-14β-isoequilenin methyl ethers[64].



Scheme 9.

It is obvious that following the general dienamine approach, as outlined above a variety of heterocyclic steroids, modified in ring A and/or B, could in principle be constructed. *U. K. Pandit*, who initiated the dienamine approach in our laboratory, is currently elaborating the method in various directions. Following the same principle, he recently has also succeeded in synthesizing the carbocyclic β-nor-steroidal skeleton *(107)*[65] (Scheme 9).

In conclusion, I would like to express my sincere thanks to my associates, Dr U. K. Pandit and Dr W. N. Speckamp, who have initiated and guided so many research problems to a successful end. I also wish to thank my other collaborators who have contributed so much to the subjects I have discussed in this paper: Mrs Drs J. L. van Bruynsvoort-Meray, Mrs Drs M. A. Th. Dzcubas-Sluyter, Mrs K. de Jonge, Drs M. A. Douw, Drs H. Evers, Drs J. C. Hubert, Drs H. de Koning, Drs W. M. B. Könst, Drs G. C. Pietzsch, Dr M. J. M. Pollmann, Dr J. A. van Velthuysen, Dr E. R. de Waard, Dr J. G. Westra, and Dr W. A. Zunnebeld.

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Chemical Bonding in Solids[**]

By Hermann Hartmann[*]

The most important of the current quantum-mechanical models of solids can be divided into one-electron (band) models and incomplete polyelectron theories. There are no complete polyelectron theories at present. However, the interatomic exchange forces become less important in lattices with high coordination numbers; a theory of metallic phases can therefore be developed, in principle, on the basis that the antisymmetrization is only local in atoms or groups of atoms.

The question of the chemical bonding in solids is simply the question of their energy content in their lowest energy state, all the free atoms in their ground states being taken as the reference point. The state of lowest energy of a solid is the equilibrium state reached in the vicinity of the absolute zero of temperature. The energy content of the solid for this case is denoted by E_0.

It is fairly certain that E_0 can fundamentally be found, apart from relativistic corrections, with the aid of quantum mechanics. However, only approximate calculations are possible in practice. Such calculations generally involve the introduction of simplifying assumptions, so that one is ultimately dealing not with the solids themselves but with models that are more or less similar to the solids.

One assumption that is nearly always introduced in connection with solids is the separation of the movements of the nuclei and of the electrons, which was shown by *Born* and *Oppenheimer* to be plausible in view of the large difference in mass between atomic nuclei and electrons[1]. The motion of the electrons is thus first treated in relation to stationary atomic nuclei; in particular, the energy of the ground state of the electrons E_E, which is increased by a quantity corresponding to the interaction energy of the supposedly stationary nuclei, is determined as a function of the coordinates describing the positions of the nuclei, which we shall denote by τ_1, τ_2, *etc.*

If this function

$$E_E = E_E(\tau_1, \tau_2, \ldots) \tag{1}$$

has an absolute minimum with the value

$$E_{E0} = E_E(\tau_{10}, \tau_{20}, \ldots) \tag{2}$$

at the point $\tau_1 = \tau_{10}$, $\tau_2 = \tau_{20}$, *etc.*, the set of atoms present in the reference state are said to be capable of forming a stable condensate.

The nuclear motion is dealt with in the next step, the function (1) now assuming the role of a potential energy. If the energy corresponding to the state of nuclear motion with the lowest energy is E_{K0}, then

$$E_0 \approx E_{E0} + E_{K0} \tag{3}$$

in the Born-Oppenheimer approximation.

If the entire treatment is repeated after introduction of additional external and possibly time-dependent forces (which can be described by parameters), it is possible to give criteria for the function that replaces eq. (2), *i.e.*

$$E^*_{E0} = E^*_E(\tau_{10}, \tau_{20}, \ldots c, t) \tag{4}$$

on the basis of which stable condensates could be designated as solid or liquid, according to their fluidity. Since the fluidity properties provide only a problematic basis for the definition of "solids", it is more convenient to refer to a stable condensate as a solid if τ_{10}, τ_{20}, *etc.* in eq. (2), apart from small nonsystematic deviations, denote lattice points in a three-dimensionally periodic arrangement of the atomic nuclei.

The function E_{E0} (2) provides information on the geometry of the solid when the atomic nuclei occupy their "normal positions". It describes the lattice type of the phase that is stable at absolute zero.

If one is interested in solids that are stable only under other conditions (temperature different from zero and presence of external forces), the calculations indicated above must initially be carried out with inclusion of the external forces. It is then necessary, however, to determine not only the ground states for the motion both of the electrons and of the nuclei but also the excited states, and subsequently to determine the normal properties of the system under the given conditions by the known methods of statistical mechanics. Relative minima of the function E_E (1) may be of some importance at finite temperatures. These minima, which are described *e.g.* by the values τ'_{10}, τ'_{20}, *etc.*, τ''_{10}, τ''_{20}, *etc.* of the coordinates, generally correspond to lattices with different geometries.

In the theoretical chemistry of solids, interest has so far been concentrated mainly on the determination of the function E_E (1). In most investigations, in fact, the normal positions τ_{10}, τ_{20}, *etc.* were determined experimentally, or else it was assumed to be necessary to determine only a common factor of these quantities. The latter procedure means that the lattice type is given and the lattice constants are regarded as the quantities to be determined.

In most cases, therefore, attempts were made to determine the energy

$$E_{E0} = E_E(\tau_{10}, \tau_{20}, \ldots)$$

(for given τ_{10}, τ_{20}, *etc.*), or after introduction of

$$\tau_{i0} = \sigma\rho_{i0}$$

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attempts were made to find the value σ_0 of σ that minimizes the function

$$E_E(\sigma\rho_{10}, \sigma\rho_{20}, \ldots)$$

for a given ρ_{i0}, *i.e.* to find the value of σ_0 such that

$$E_{E0} = E_E(\sigma_0\rho_{10}, \sigma_0\rho_{20}, \ldots).$$

Two methods have been used for the solution of these problems:

1. Treatment of the solid as a one-electron problem and subsequent formulation of the electronic ground state of the solid in accordance with the Aufbau principle ("filling" of the one-electron states with electrons in accordance with Pauli's exclusion principle).

2. Treatment of the solid as a true many-electron problem.

In method 1, the potential energy of the electron system, including the interaction energy of the fixed atomic nuclei, is

$$V = -\sum_i\sum_j \frac{Z_j e^2}{r_{ij}} + \sum_i\sum_{i<i'} \frac{e^2}{r_{ii'}} + \sum_j\sum_{j<j'} \frac{Z_j Z_{j'} e^2}{r_{jj'}} \tag{4}$$

where j (or j') is a number indentifying an atomic nucleus and i (or i') is a number identifying an electron; Z_j (or $Z_{j'}$) is the number of charges on the j-th (or j'-th) atomic nucleus and e is the elementary charge. The first sum in eq. (4) represents the interaction energy of the electrons with the nuclei, the second that of the electrons with one another, and the third that of the nuclei with one another. V thus depends in a very complicated manner on the coordinates of all the nuclei and of all the electrons.

Any given electron is in interaction with all the (stationary) nuclei and with all the other electrons. Since the motion of these other electrons is periodic in the final analysis (they would otherwise escape from a finite solid body), it is reasonable to imagine an interaction energy of the chosen electron with the other electrons that is averaged over time, and which then depends only on the position of this electron. If the interaction of the electron with the nuclei is added to this interaction, it is reasonable to picture the electron as moving in an "effective" electric field, so that its effective potential energy can be expressed by

$$v = v(q)$$

where q is a symbol for the three coordinates of the electron.

The expression

$$V_{eff} = \sum_i v(q_i) \tag{5}$$

would then give the effective potential energy of the electron system. A well-known procedure[2] nowadays is to collect the terms in

$$V = V_{eff} + (V - V_{eff}) \tag{6}$$

as indicated and to choose v such that $|V - V_{eff}|$ is generally, *i.e.* for most configurations, small in relation to $|V_{eff}|$. Then

$$V \approx V_{eff} = \sum_i v(q_i) \tag{7}$$

The Schrödinger equation with this expression as the potential energy can be obtained immediately, and in order to find the one-electron states and their energy values ε, one need only solve the representative one-electron Schrödinger equation

$$-\frac{\hbar^2}{2m}\Delta\psi + v(q)\psi = \varepsilon\psi \tag{8}$$

To improve the ε values, a perturbation calculation must be carried out with the eigenfunctions of eq. (8) and $(V - V_{eff})$ as perturbation operators.

All one-electron theories of solids are based on this scheme. The simplest approximation with $v(q) = \text{const.}$ is the Sommerfeld theory[3]. *Peierls*' theory[4] is based on a weakly periodic v, and *Bloch*'s theory[5] on a strongly periodic v. An additional assumption regarding the form of the eigenfunction of eq. (8) is that introduced by *Wigner* and *Seitz*[6]. *Slater*'s extensions of the *Wigner-Seitz* approach, *e.g. Slater*'s method of augmented plane waves[7], are also based on eq. (8) and its conditions. The methods mentioned are known collectively as band theories.

A point to which insufficient thought is often given is the need to recognize clearly, in the application of the one-electron theories, that the function $v = v(q)$ that describes the effective field can only be chosen plausibly, but does not itself occur in nature, and thus is not definite. It is unequivocally a model relation, and this means that its (plausible) application gives a model that is not identical with the solid.

As to method 2, there are as yet no complete polyelectron theories of solids.

Eigenfunctions of polyelectron systems depend on the coordinates of all the electrons:

$$\psi = \psi(q_1, q_2, \ldots) \tag{9}$$

They must be antisymmetric. If T is an operator by which the coordinates of two electrons are interchanged in ψ, then

$$T\psi = -\psi \tag{10}$$

must be valid for all such interchanges.

Theories in which only local antisymmetrization in atoms or groups of atoms is introduced as an approximation must be described as incomplete polyelectron theories. If the atoms or groups of atoms in question are denoted by the subscript k, one can write

$$\psi = \psi_1\psi_2\cdots = \prod_k \psi_k \tag{11}$$

where ψ_k is an antisymmetric eigenfunction of an atom or of a group of atoms. The complete function ψ (11) is not completely antisymmetric under these conditions.

From the standpoint of the valence structure approximation[8], the assumption of only local antisymmetrization is equivalent to ignoring exchange interactions between different atoms or groups. Empirical parameters, *e.g.* "ionic radii", are introduced in some cases to compensate for this.

This group of theories includes in particular the Madelung theory[9] of ionic crystals and its extension by *Hund* and *Heisenberg* through the inclusion of polarization effects[10]. The crystal field theory[12], which acquired new life from the success of the methodically equivalent ligand field theory[11], deals with polarization effects in incomplete shells.

As I pointed out a long time ago[13], the interatomic exchange effects become less important on purely combinatorial grounds in lattices with high coordination numbers. In principle, therefore, a theory of metallic phases can be developed on the basis of only local antisymmetrization. Investigations on magnesium and zinc are in progress. An investigation on inert-gas crystals[14] also belongs to this field.

Interatomic as well as intraatomic exchange effects are taken into account in the statistical treatments of solids, which ultimately arise from the work of *Lenz* and *Jensen*[15]. However, since quantum mechanics is used only for averaging in statistical studies, these again cannot be described as complete polyelectron theories.

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Gamma Resonance Spectroscopy and Chemical Bonding[**]

By Rudolf L. Mössbauer[*]

Gamma resonance spectroscopy makes it possible to observe directly hyperfine interactions in solids. In the field of chemistry the feature of greatest interest is the measurement of isomeric shifts of gamma lines because these shifts are proportional to the electron density at the nucleus and can thus give detailed information about the electronic structure of the chemical bond. After a brief introduction to gamma resonance spectroscopy, this paper deals with the fundamental problem of the interpretation of measured isomeric shifts in terms of electron densities and then gives representative examples of chemical information that can be obtained for transition elements from the shifts and the splitting of the gamma lines.

1. Introduction

Gamma resonance spectroscopy is based on the possibility of observing in solids gamma emission and absorption lines of natural width, *i.e.* lines with a frequency definition as much as ten orders of magnitude sharper than that achieved in the commonly observed broadening of gamma lines due to the Doppler effect[1]. The method is restricted to relatively low-energy gamma transitions and often requires the use of low temperatures to minimize the background of nonresonant gamma radiation which is always present outside the range of the natural line widths[2]. Figure 1 gives a summary of those elements for which gamma resonance spectroscopy has so far been possible. A characteristic feature is the absence of any light elements. Figure 1 also shows, however, that gamma resonance spectroscopic measurements can be carried out in all series of transition elements. Figure 2 illustrates the principle of measurements of this kind.

The hyperfine interactions between the electric and magnetic moments of the atomic nuclei and the fields which act on them in solids lead to shifting and splitting of the nuclear levels, which can appear as isomeric shifts and

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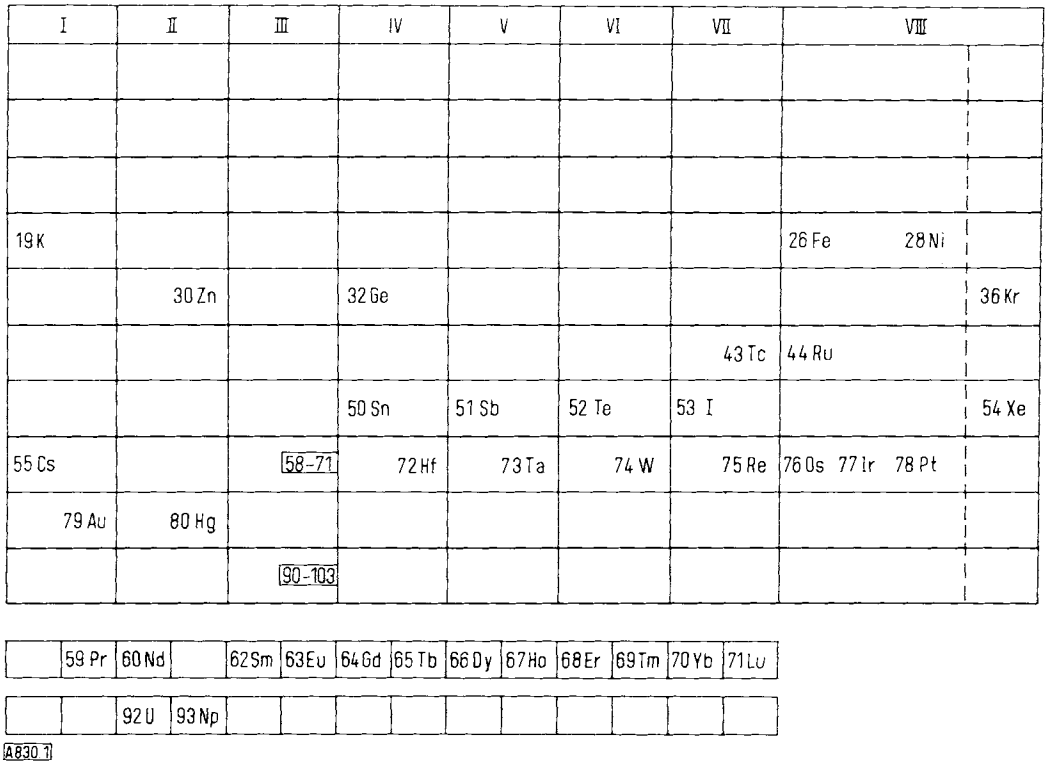


Fig. 1. Summary of those elements with which gamma resonance spectroscopy has so far been possible. For many elements usable gamma transitions exist in several isotopes and at different energies.

magnetic dipole or electric quadrupole splitting of the gamma lines. While under normal circumstances these changes in the frequency of gamma lines due to hyperfine interactions are completely swamped by the latter's Doppler broadening, the method of resonance spectroscopy often makes it possible to observe directly the frequency changes because of the increased resolution due to the use of natural line widths. In chemistry it is primarily the study of isomeric shifts and quadrupole splitting of the gamma lines that is of interest. In what follows we shall

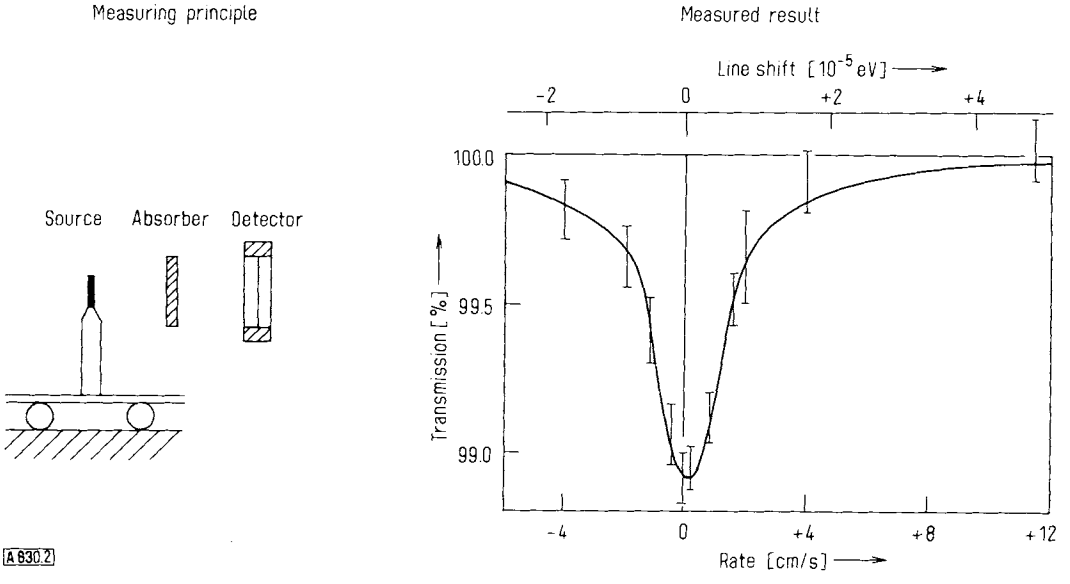


Fig. 2. Principle of the measurements in gamma resonance spectroscopy. The left-hand part of the figure shows the experimental arrangement, consisting of a radioactive source and a resonance absorber with atomic nuclei identical to those in the gamma source. The source and the absorber are often placed in a low-temperature cryostat. The detector measures the gamma radiation passing through the absorber as a function of the relative velocity between the source and the absorber, which is generally produced by means of an electromagnetic drive system. The result of such a measurement is shown on the right-hand side of the figure: a resonance absorption maximum, *i.e.* a minimum in the intensity received at the detector, occurs at zero relative velocity of the source and the absorber, at which the source and the absorber are exactly in resonance and thus have the same fundamental frequency. This perfect resonance absorption can be disturbed by exploiting the linear Doppler effect: a change in the relative velocity of the source and the absorber causes a reduction of the resonance absorption and hence a corresponding increase in the intensity recorded by the detector. In this way with an emission line having a natural line width Γ we spread an absorption line of the same natural line width and obtain for the recorded intensity, in the ideal case, a line width $2\,\Gamma$ [2b].

discuss the methods and the chemical information content of such studies. The discussion of practical examples will be restricted to stable compounds of the 3d-, 4d-, and 5d transition elements[3].

2. Isomeric Shifts of Gamma Lines

A system consisting of a nucleus and an electron shell will be in a state of minimum energy if the nuclear charge is concentrated at a point. Any increase in the charge radius of a nucleus, or indeed any increase in the electron density at a nucleus of finite extent, leads to an increase in the energy of the total system. Thus, the energetic position of any nuclear level of a nucleus incorporated in a solid depends both on the nuclear radius and on the electron density at the nucleus. There is a similar dependence for the frequencies of the gamma transitions between the individual nuclear levels. In analogy to the optical isotopic shift, the isomeric shift is given by:

$$S_a - S_b = (v_a/c)E_0 - (v_b/c)E_0 = C\{|\psi(0)|_a^2 - |\psi(0)|_b^2\} \quad (1)$$

where $S_a - S_b$ is the energy shift of two gamma lines, with respect to one another, for a gamma transition of energy E_0 in one and the same nuclear isotope, situated in two different chemical environments a and b, while $v_a - v_b$ represents the difference of the Doppler velocities for the two compounds. The quantity $|\psi(0)|^2$ represents the total nonrelativistic electron density at the site of the nucleus. The constant C, which is a characteristic of the nuclear radiating transition in question, is a function of the charge distributions of the nucleus in the initial and final states. Assuming a uniform nuclear charge distribution, a good approximation is:

$$C = (2\pi/5)Ze^2(R_1^2 - R_0^2)S'(Z) = (4\pi/5)Ze^2R^2(\Delta R/R)S'(Z) \quad (2)$$

where R_0 and R_1 denote the charge radii of the ground state and of the first excited state respectively; $R = (R_1 + R_0)/2$. $S'(Z)$ is a correction factor calculated approximately by *Bodmer*[4], which takes into account the modification of the nonrelativistic electron density due to relativistic effects, in particular the variations in the wave functions in the region of the nucleus. A table of values of $S'(Z)$ for all atomic numbers Z has been given by *Shirley*[5]. It must be emphasized that the factor $S'(Z)$ does not in any way represent a conversion factor that would allow a conversion of the nonrelativistic wave functions occurring in equation (1) at the position of the nucleus into a relativistic type.

Only the s electrons of the outermost electron shell, *i.e.* the shell which directly takes part in chemical bonding, contribute directly to the total electron densities appearing as a difference in eq. (1). Measurements of the isomeric shift thus give direct information on the proportion of s electrons in a chemical bond. In the case of heavy nuclei the relativistic $p_{1/2}$ electrons can also give considerable probability densities at the nucleus, but in many cases there will be no substantial difference in the occupancy of the $p_{1/2}$ shells, so that the contribution of the $p_{1/2}$ electrons to isomeric shifts can be neglected in most cases.

While the s electrons make direct contributions to the electron density at the nucleus, the electrons in partially filled shells, such as occur in the transition elements, contribute indirectly to the isomeric shifts, by the "screening effect" they have on the s electrons.

As will be explained later, it is often difficult to break down a measured isomeric shift into the contributions originating directly from s electrons and indirectly from screening non-s-electrons.

A study of isomeric shifts can be carried out in all series of nd-transition elements. For this purpose the most suitable transition in the range of 3d-elements is the 14.4-keV transition in ^{57}Fe, in the 4d-element range the 90-keV transition in ^{99}Ru, while in the range of 5d elements the most suitable are the 73-keV transition in ^{193}Ir, the 36-keV transition in ^{189}Os, and the 77-keV transition in ^{197}Au.

2.1. The Problem of Calibrating the Isomeric Shift

Measurements of isomeric shifts yield, as can be seen in equation (1), a factor C which originates in the physics of the nucleus and an electronic factor $\Delta|\psi(0)|^2$, the total nonrelativistic electron density difference at the nucleus for two different compounds. There is as yet no known method of measuring these two factors separately. To determine one of the two factors, therefore, one is obliged to find the other by calculation. In practice, in the present state of the art, a measurement is first carried out of the isomeric shift of a selected nuclear isotope for two different valence states of the electron shells. Comparison of the measured values with the electron densities calculated for the two valence states then gives directly the value of C which is specific to the particular nuclear transition, *i.e.* essentially the quantity $\Delta R/R$. This determination of C is a central problem in the interpretation of measured isomeric shifts. Solution of this problem makes it possible to establish for the nuclear transition considered a practically linear relationship between the isomeric shifts and the electron densities at the nucleus, a process usually described as calibration of the isomeric shift. Once the calibration constant C has been determined, total electron densities can be found directly for the whole enormous complex of chemical compounds in which the nuclear transition concerned can be measured. The electron densities at the nucleus are often a sensitive indication of the effective valence state of the atom measured. In this way information on the nature of chemical bonding can be obtained directly from the isomeric shifts.

The difficulty that arises in the method of calibration described above lies in the fact that while it is possible in principle to carry out reliable Hartree-Fock calculations of electron densities at the nucleus, such calculations presuppose a knowledge of the real electron configurations of the atoms or ions considered. While these configurations are generally known for free particles, the corresponding information is often lacking in the case of ions incorporated in solids, in which the isomeric shifts are actually measured. For calibration purposes therefore, as a general principle,

compound pairs in which the electron configurations are more or less certain are chosen, as for example in purely ionic compounds. Deviations from this ideal state, which is never achieved in practice, give rise to errors in the calibration constant C. Such errors, are however, of secondary importance if one is mainly interested in drawing qualitative conclusions about the nature of the chemical bonding, for example in systematic trends in a large series of compounds. For quantitative conclusions a precise determination of C is essential, and this problem has not so far been satisfactorily solved.

2.2. Isomeric Shifts in 3d Transition Elements: The 14.4-keV Transition in ^{57}Fe

As an illustration of the difficulty of the calibration problem Table 1 gives a collection of diverse values given for the ratio $\Delta R/R$ in the 14.4-keV transition in ^{57}Fe by various investigators. Table 2 gives values of nonrelativistic electron densities $|\psi(0)|^2$ for the most important configurations of iron. The differences in the s-electron densities at the nucleus are due to the screening effect of 3d electrons on the s electrons. This screening effect apparently acts mainly on the 3s electrons, while the s electrons in the two inner shells are hardly affected by it.

Table 1. Relative change in the nuclear radius $\Delta R/R$ for the 14.4-keV transition in ^{57}Fe.

Method	$\Delta R/R$	Ref.
Measurements on Fe^{II} and Fe^{III} compounds of highest ionicity	-1.8×10^{-3}	[6]
Deduction using effective charges from X-ray absorption measurements	-5.0×10^{-4}	[8]
Combination of optical data and MO calculations	-8.5×10^{-4}	[9]
MO calculation taking into account the screening by 4d- and 4p electrons	-9.0×10^{-4}	[10]
Comparison of the calculation of inner electron polarization with high-pressure measurements	-4.0×10^{-4} -5.2×10^{-4}	[11] [12]

The values of $\Delta R/R$ given were calculated with the aid of the nonrelativistic wave functions calculated by *Watson* [7]. To take into account the relativistic corrections for the s-electron densities, all values of $\Delta R/R$ in the table must be reduced by the factor $S'(Z)=1.33$.

Table 2. $|\psi(0)|^2$ in units of the cubic Bohr radius a_0^3 for electrons with the same spin orientation, after *Watson* [7].

Configuration	$Fe(3d^64s^2)$	$Fe^{2+}(d^6)$	$Fe^{3+}(d^5)$	$\lvert\psi(0)\rvert^2(d^6)-\lvert\psi(0)\rvert^2(d^5)$
1s	5377.873	5377.840	5377.625	0.215
2s	493.968	493.796	493.793	0.003
3s	68.028	68.274	69.433	−1.159
4s	3.042			

In their calibration of the isomeric shift in ^{57}Fe, *Walker et al.*[6] assumed that the iron ions in the complex salts of highest ionicity, *e.g.* in $Fe_2(SO_4)_3\cdot6H_2O$ or in $FeSO_4\cdot7H_2O$, can be associated with pure d^5- or d^6 configurations. For Fe^{III} at least this assumption is very suspect, since in this case the iron ion would have to carry three units of charge, a condition that seems to be very difficult to realize. In fact, on the basis of X-ray absorption measurements, *Goldanskii*[8] arrived at effective charges of +1.9 for Fe^{II} and only +1.2 for Fe^{III}. *Jørgensen*[13] calculated, from optical data, an effective charge of +1.7 for Fe^{III} in high-spin complexes. From self-consistent charge and configuration MO calculations, *Viste et al.*[14] obtained, among other things, for $[Fe^{III}F_6]^{3-}$ a 4s population of iron equal to 0.32. On the basis of these results, *Danon*[9] used a $3d^54s^{0.32}$ configuration for $[Fe^{III}F_6]^{3-}$ and a $3d^6$ configuration for the Fe^{II} complex of highest ionicity, and hence arrived at the value of $\Delta R/R$ given in Table 1.

Special interest attaches to the low-spin iron complexes, which are often distinguished by the absence of isomeric shifts between the formal di- and trivalent states of the iron. Classic examples of this are the complexes $[Fe^{II}(CN)_6]^{4-}$ and $[Fe^{III}(CN)_6]^{3-}$, which exhibit only a slight mutual isomeric shift. A possible interpretation is back bonding, *i.e.* the transfer of electrons from the metal ion to empty π^* antibonding orbitals of the ligands. A transfer difference of one electron between Fe^{2+} and Fe^{3+} might explain the absence of isomeric shifts in the low-spin $3d^5$- and $3d^6$ configurations of the cyano-complexes but, as will be shown in greater detail later, this hypothesis is surely too simple.

2.3. Isomeric Shifts in the 4d Transition Elements: The 90-keV Transition in ^{99}Ru

Measurements of the isomeric shift in ruthenium compounds enable observations to be made over an unusually wide range of different valence states. Figure 3 shows three

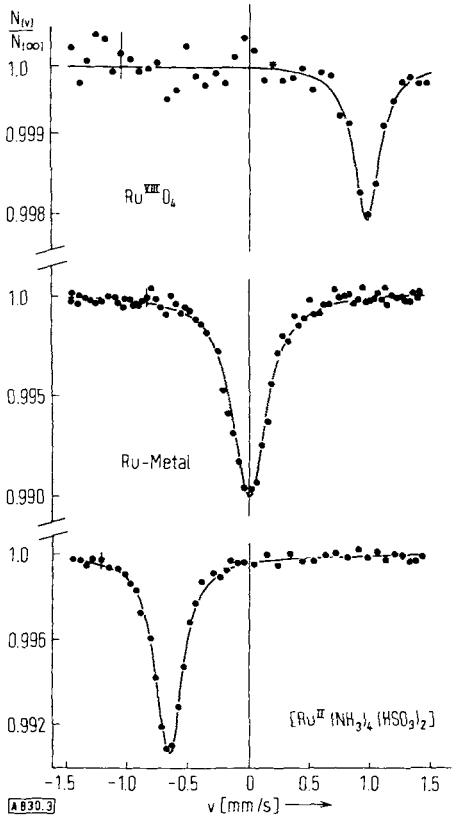


Fig. 3. Gamma resonance spectra of ruthenium compounds, measured at 4.2 °K for the 90-keV gamma transition in ^{99}Ru, using a metal source exhibiting no hyperfine splitting [15].

representative spectra and Figure 4 a graphical representation of the results of some measurements of isomeric shifts[15]. The isomeric shift is decisively influenced by the charge transfers which arise in the formation of molecular

measured at the nucleus of M, insofar as s electrons are transferred; otherwise there is a decrease. The individual effects that occur can best be seen from an MO scheme, as represented in Figure 6 for the case of an octahedral

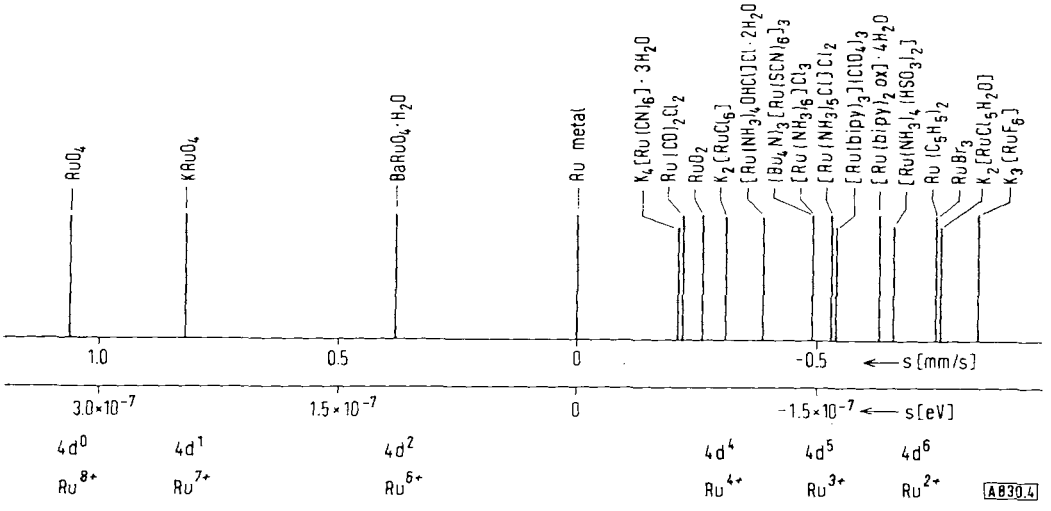


Fig. 4. Isomeric shifts of the 90-keV gamma radiation from ^{99}Ru for various compounds of ruthenium, relative to metallic Ru (reference point). The lower part of the figure shows the formal valence states and the formal electron configurations of the Ru ions in the compounds investigated [15].

orbitals from the metal orbitals and ligand orbitals. This is demonstrated in Figure 5, where a metal orbital and a ligand orbital, both of which belong to the same irreducible representation, combine to form a bonding and an antibonding molecular orbital. An increase in the bonding increases the distance between the two molecular orbitals.

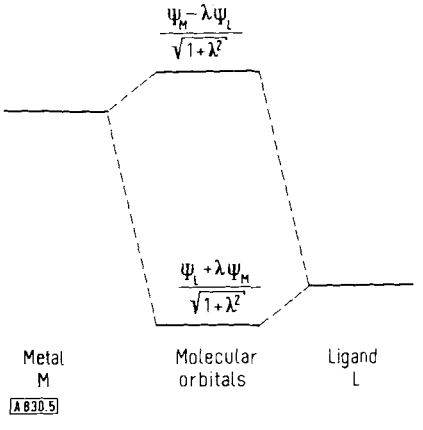


Fig. 5. Combination of a metal orbital and a ligand orbital to form a pair of molecular orbitals (MO). The coupling increases with increasing λ. Overlap contributions have been neglected. In the bonding MO an increase in λ corresponds to an L→M charge transfer, in the antibonding orbital to an M→L transfer.

The bonding orbital here assumes a more marked M character, this corresponding to a charge transfer L→M, while the opposite applies to the antibonding orbital. For the same occupancy of the two orbitals there is no charge transfer at all with increasing coupling. A lower occupancy of the metal orbital, placed higher by chance in Figure 5, on the other hand, leads to increasing charge transfer on coupling, which is in the direction L→M in the example chosen. The result is an increase in the isomeric shift

environmental symmetry. This type of symmetry is found in the majority of the compounds given in Figure 4. It should be observed that the position of the metal orbital

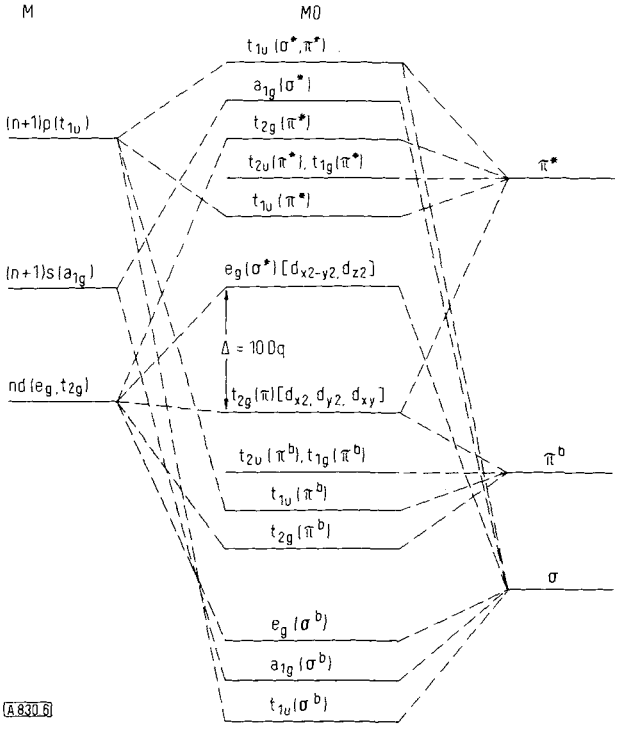


Fig. 6. MO level scheme for octahedral metal complexes for ligands with internal π-bonding [16].

in Figure 6 is determined by the actual electron configuration of the metal ion, and therefore does not correspond to the configuration of the free ion. Details of the level structure, for the given case of $n=4$ for ruthenium, are certainly considerably influenced by the strong spin-orbital

coupling, so that the following remarks can only have a qualitative character.

For an octahedral environmental symmetry of the central Ru ion, there is a splitting of the 4d shell, which is relevant to the optical and magnetic characteristics, leading to $t_{2g}(\pi)$ and $e_g(\sigma)$ molecular orbitals. The different states of oxidation are distinguished by different occupancies of the t_{2g} state. Thus, for example, for the octahedral complexes of Ru^{II}, Ru^{III}, and Ru^{IV} the formal configurations $(t_{2g})^6$, $(t_{2g})^5$, and $(t_{2g})^4$ apply.

The rise in the electron densities $|\psi(0)|^2$ with increasing valence which can be seen in Figure 4 can be ascribed qualitatively to the parallel process of a decrease of 4d electrons *i.e.* the progressive reduction of the screening of s electrons, in the inner shells. However, this view is in no way conclusive, for increasing occupancy of 5s orbitals could equally be assumed. In fact, in a quantitative description all electron-transfer processes between the ligands and the metal ion must be taken into account. Table 3 gives a summary of the more important of these processes, which in ruthenium can appear as a result of the coupling of ligand and metal orbitals to molecular orbitals and thereby lead to a change in the electron density at the nucleus. It is the differences in the contributions of these different electron-transfer processes which give rise to differences between the isomeric shifts of compounds having the same formal valence. Leaving this aside, Figure 4 demonstrates the possibility of classifying the valences of ruthenium in its complexes from measurements of the isomeric shifts. Only $K_4[Ru(CN)_6]\cdot 3H_2O$, $K_4[Ru(CN)_6]$, and $RuBr_3$ appear to behave differently. For the first two compounds a marked occurrence of a type of bonding designated as back-bonding can be assumed, in which the t_{2g} orbitals undergo considerable coupling with initially unoccupied antibonding π^*-ligand orbitals. According to *Shulman et al.*[17], such an effect can cause a marked abstraction of electrons from the metal ion and thus explain the fact that isomeric shifts of the two hexacyano-complexes should not be associated with the nominally divalent but with the nominally tetravalent state of ruthenium, corresponding to the transfer of two electronic charges from the metal to the ligands. In fact, measurements of isomeric shifts directly point to the existence of marked back-bonding. Thus, isomeric shift data are really predestined for a classification of chemical valences.

Table 3. Change of electron density at the nucleus and electron-transfer process for octahedral symmetry.

	Electron-transfer process	$\Delta\|\psi(0)\|^2$
1.	$\sigma_L \rightarrow \sigma_M(4d)$	<0
2.	$\pi_L \rightarrow \pi_M(4d)$	<0
3.	$\pi_M(4d) \rightarrow \pi_L$	>0
4.	$\sigma_L \rightarrow \sigma_M(5s)$	>0
5.	$\sigma_L, \pi_L \rightarrow \sigma_M(5p), \pi_M(5p)$	<0

The measured isomeric shift in $RuBr_3$ corresponding to a nominally divalent state cannot be interpreted at all unambiguously. However, this compound exhibits diamagnetic behavior, which is quite unusual for a formal $(t_{2g})^5$ configuration.

2.4. Isomer Shift Measurement under High Pressure

Isomeric shifts are usually observed in different chemical compounds, the bonding state, which is characterized by a large number of parameters, being varied in steps. If, however, the isomeric shifts are measured as a function of pressure, continuous variation of the bonding parameters over a wide range in one and the same compound can be achieved. Such high-pressure studies have so far been almost exclusively restricted to those isotopes that can be measured at normal temperatures, since the considerable experimental problems of low-temperature high-pressure resonance spectroscopy have not yet been satisfactorily solved.

Drickamer et al.[18] carried out a study of isomeric shifts, in particular on compounds of iron, and by comparison with optical studies obtained valuable information on the chemical behavior of iron. For example, in many cases the measurements showed increasing reversible reduction, as the pressure was increased, of high-spin Fe^{III} into Fe^{II}, for example in $Fe_2(SO_4)_3$, $FePO_4$, and Fe(III) citrate. They interpret this reduction as the result of a progressive lowering with compression of the ground state orbitals of the metal relative to the ligand orbitals, which facilitates thermal electron transfer, *i.e.* an L→M electron transition from a ligand orbital bonding weakly or not at all to a 3d-metal orbital, with the establishment of thermal equilibrium. The pressure-induced reduction is thus not associated with a transition point; instead the electron transfer made possible by the pressure causes reduction at a single ion, with simultaneous electrical and mechanical disturbance of the adjacent ions, the reducibility of which is thereby decreased. Increasing pressure thus favors electron transfer, but on the other hand it leads to an increased inhibition of reduction in adjacent ions.

The strongly covalent low-spin iron complexes exhibit a particularly interesting pressure-dependent behavior, the most striking representatives being the cyanoferrates(II) and -(III), and their derivatives. At pressures around 200 kbar and temperatures around 150°C, *Drickamer*'s experiments with salts such as K_4X, Na_4X, Zn_2X, Ni_2X, and Cu_2X (where $X=[Fe(CN)_6]$), showed a low-spin → high-spin conversion. This is contrary to the naive expectation that with increasing pressure an increase in the crystal electric field should favor a high-spin → low-spin transition. According to *Drickamer et al.*[18], this precisely opposite effect is due to a lowering of the metal orbitals relative to the weakly bonding or nonbonding ligand orbitals. This also signifies an increase in the energetic distance between metal orbitals and antibonding (π^*) ligand orbitals. In parallel with this process there is a reduction of the back-bonding effect, whereby the metal-cyanide bonding is weakened.

In the case of the high-spin iron complexes, *Drickamer et al.*[18] found that the electron density at the nucleus increases with increasing pressure. To interpret this they assumed a radial expansion of the 3d electrons increasing with pressure, with a consequent reduction of the 3d-3s screening and hence an increase in the s-electron density at the nucleus. In this interpretation the predominant part

in the variation of the isomeric shift with pressure is ascribed to the screening 3d electrons. Making the reasonable assumption of increasing covalency with increasing pressure, with purely 3d-electron participation in the bonding we are really dealing with an M→L electron transfer in the antibonding orbitals which is also manifested in a reduction of the optically observed Racah parameters. At the same time, however, an overcompensating L→M transfer occurs in the bonding orbitals, so that overall there is an increase in the screening effect and hence a reduction of the electron density $|\psi(0)|^2$, contrary to the experimental findings. It is therefore reasonable to assume participation of 4s electrons in the bonding, so that a small L→M transfer is sufficient to explain the sign of the pressure dependence of the isomeric shift observed experimentally. The assumption of 4s participation in the bonding is indeed the basis of the calibration of the isomeric shift in ^{57}Fe carried out by *Danon*, *Goldanskii*, and *Šimánek et al.* and given in Table 1.

Šimánek et al.[11,12] attempted a calibration of the isomeric shift in the case of the 14.4-keV transition in ^{57}Fe by comparing experimental data with theoretical calculations of the variation with pressure. This work is of interest mainly because the calculations gave as the preponderant effect for the occurrence of the isomeric shift the overlapping of the ligand orbitals with the closed 1s-, 2s-, and 3s shells of the iron ion. Such overlap contribution to the isomeric shift is a direct consequence of the Pauli principle, which would exclude the electrons from the overlap region of s-metal orbitals and ligand orbitals and hence cause an increase in the electron density at the nucleus due to s-metal orbitals. Mathematically, this overlap effect, which can be calculated on the basis of the Heitler-London model, can be described by orthogonalization of the ligand orbitals relative to the filled s-metal orbitals. According to *Šimánek et al.*[11,12], the predominant mechanism for the increase of electron density at the nucleus with increasing pressure is also given by the overlap effect, through its strong dependence on the distances between metal ions and ligands. This is indeed valid if a contribution due to 4s electrons can be neglected, as is the case with many compounds of Fe^{II}. On the other hand, in ionic compounds of trivalent iron the contribution of the 4s electrons cannot be neglected. Here the overlap effect even leads to an increase in the direct contribution of the 4s electrons to the isomeric shift, so that the contribution of the 4s electrons becomes preponderant. Quantitative follow-up of this reasoning, such as was carried out by *Šimánek et al.* for the examples of FeO and $KFeF_3$, suffers especially from the inadequate knowledge of the modifications which the ligand orbitals used for the calculation of the overlap undergo in solids as compared with the atomic case.

Finally, it should be emphasized that the overlap effect described by *Šimánek et al.* differs basically from the phenomena occurring within the framework of an MO description. It is not possible to exclude *a priori* the possibility that MO considerations may indeed yield relatively good values for energy levels which are amenable to optical experiments, but only a poor approximation for the interpretation of isomeric shift data if overlap effects of the kind outlined here really make the predominant contribution.

2.5. Isomeric Shift and Chemical Systematics

In qualitative interpretations it is frequently attempted to correlate the measured isomeric shifts of a large range of chemical compounds of one and the same nuclear isotope systematically with suitable parameters. In this way it is often possible to establish a relationship between the isomeric shifts and electronegativity differences. However, such a single-parameter correlation is only meaningful, if at all, when it is restricted to isomorphous compounds which differ only in the degree of ionization and not in the nature of the bond.

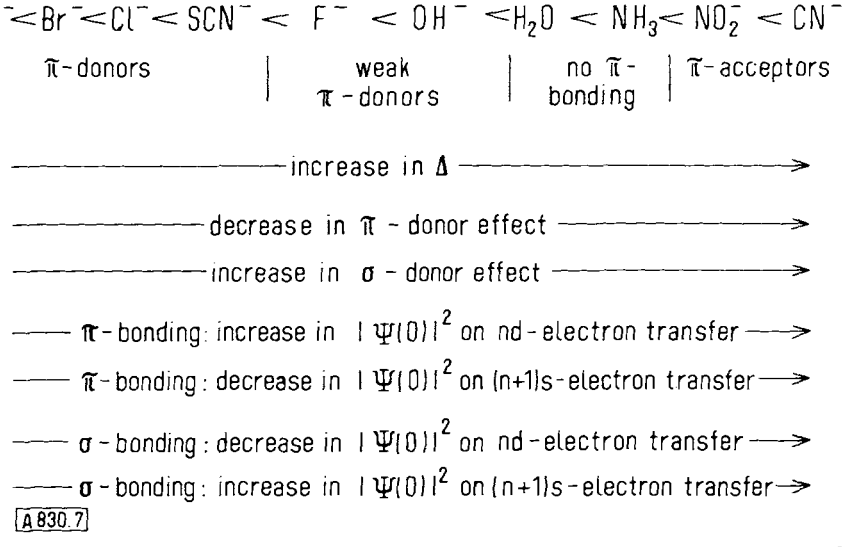


Fig. 7. Spectrochemical series of frequently occurring ligands and variation of the electron density $|\psi(0)|^2$ at the nucleus for transition elements.

For many transition-element complexes it is possible to establish for the isomeric shifts of the central metal a correlation with spectrochemical behavior, the systematics of which have resulted in the formulation of the spectrochemical series of ligands. The active parameter of this series is the splitting of the d orbitals in the ligand field, observed in absorption spectra. For example, for a given metal ion in octahedral and also in the square environmental symmetry, the splitting Δ of the d orbitals increases in accordance with the spectrochemical series given in Figure 7. This series is probably valid for other environmental symmetries.

The variation of Δ can be understood directly from the coupling constants λ (see Fig. 5). The ligands occurring in the spectrochemical series differ in their σ or π donor or acceptor properties, *i.e.* in their ability to effect electron transfers of the L→M type (donor) or M→L type (acceptor). Strongly covalent compounds are distinguished by their approximately obeying the principle of electroneutrality, this leading to a synergic coupling between the σ- and π-orbitals, in which the M→L transfer associated with strong π-acceptor capacity is more or less compensated by a correspondingly large L→M σ-donor transfer. *Graham*[19] deduced the existence of such a synergic coupling principle from the behavior of Mn complexes. At the start of the spectrochemical series there are ligands with predominant π-donor properties, which leads to destabilization of the antibonding orbitals (see Figs. 5 and 6), and hence results in smaller values of Δ. Toward the end of the series the π-donor capacity decreases, and finally changes to a π-acceptor capacity, which goes along with a σ-donor capacity; both effects lead to an increase of Δ, since the π-acceptor action stabilizes the antibonding π-orbitals while the σ-donor effect destabilizes the σ-orbitals. In connection with the isomeric shift, in charge transfers of this kind, we have to make a clear distinction between the opposing effects of d- and s electrons. Progression along the spectrochemical series involves a reduction of the L→M charge transfer caused by π bonding, and hence an increase in the isomeric shift. In parallel with this, however, there is an increase in the L→M charge transfer caused by σ bonding, which can occur by means of both s- and d-electron transfer. When the synergic coupling principle is strictly maintained, the result is in the normal case an increase in the isomeric shift in the spectrochemical series.

The optically measurable spectrochemical behavior is directly influenced by the transfer of s- and d electrons changing with the bonding. As far as the isomeric shift is concerned, s-electron transfers have a considerably larger influence than d-electron transfers. The ratio of nonrelativistic electron density changes at the nucleus which occur on the addition of an nd-electron or the subtraction of an (n+1)s-electron can be determined by Hartree-Fock calculations. If, for example, we define the change of configuration $\{\Delta nd\} = \{nd^6(n+1)s^1\} - \{nd^5(n+1)s^1\}$ or $\{\Delta(n+1)s\} = \{nd^6(n+1)s^1\} - \{nd^6\}$, we obtain for the ratio $\zeta = \delta|\psi(0)|^2_{\{\Delta(n+1)s\}}/\delta|\psi(0)|^2_{\{\Delta nd\}}$ values of approximately 2.5 for Fe, 3.1 for Ru, and 3.4 for Ir. While the proportions of s- and d-electron transfers must be given much the same weight in respect of the effective charge, in respect of the isomeric shift the s-electron transfers have the stronger effect.

Measurements of isomeric shifts do not make it possible to determine directly the relative proportions of s- and d-electron transfers as we progress along the spectrochemical series. Such a separation might, however, be possible with a knowledge of the effective charge difference, which is associated with a charge transfer $n_d(M\rightarrow L) - n_d(L\rightarrow M) - n_s(L\rightarrow M)$.

To illustrate the correlation between the isomeric shift and the spectrochemical series, Figure 8 shows a collection of the isomeric shifts for compounds of gold, using the 77-keV transition in ^{197}Au. The Au^{I} complexes have linear structures almost throughout, whereas the Au^{III} compounds exhibit a square arrangement of the ligands. The change of the isomeric shift substantially follows the spectrochemical series. A striking exception is the position of tetrafluoroaurate, although this may be due to the different coordination (CN=6). A characteristic feature of the data given in Figure 8 is that the compounds of Au^{I} and Au^{III} with the same ligands exhibit relatively small isomeric shifts with respect to one another.

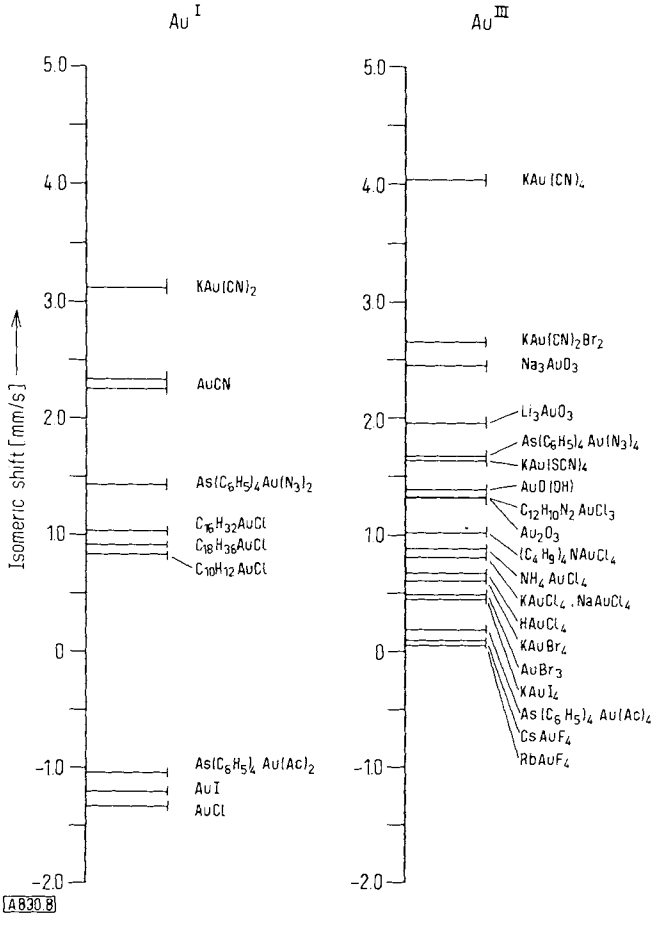


Fig. 8. Isomeric shifts of the 77-keV gamma transition in ^{197}Au for compounds of mono- and trivalent gold; after [20].

Rough estimates show that these shifts are an order of magnitude smaller than would correspond to the $5d^{10} - 5d^8$ transition, so that the actual configurations differ substanti-

ally from the formal ones. Since in the Au^{I} compounds the 3d-molecular orbitals are fully occupied, and the differences in the isomeric shift must therefore be ascribed to charge transfers to σ orbitals, it can be concluded on the basis of an MO description that in respect of the isomeric shift the screening effect of d-electron transfer is overcompensated by the direct effect of s-electron transfer.

An analogous correlation between isomeric shifts and the spectrochemical series can in general be expected for the strongly covalent complexes of the transition elements, especially the low-spin complexes. *Bancroft et al.*[21] confirmed this for a long series of low-spin complexes of Fe^{II}. For the high-spin complexes, with their often lower covalence, there should rather be a correlation with the nephelauxetic series of ligands, since this series substantially reflects the electronegativity[22]. *Danon* for example, established such a correlation for the high-spin complexes of Fe^{II}[23].

3. Relativistic Line Shifts

Relativistic time dilatation leads to a quadratic Doppler effect, which is also manifested in a shift of the gamma lines and which must therefore be taken into account in the interpretation of isomeric shifts. This relativistic line shift can be made clear on the basis of quantum mechanics[24]. The emission of a gamma quantum of energy E_0 corresponds to a mass loss $\Delta m = E_0^2/mc^2$ on the part of the emitting nucleus. This results in a slight increase in the internal energy of the lattice, with an equal decrease in the energy of the emitted quantum, *i. e.* the relativistic line shift ΔE. The applicable relation is $\Delta E = -E_0 \Delta E_{mol}/(2N_L mc^2)$, where ΔE_{mol} is the change of internal energy of the crystal per mole, N_L is Avagadro's number, and m is the mass of the emitting nucleus. Expressed in terms of Doppler velocities v and the internal energies of two compounds 1 and 2, $v_{relativistic} = E_{mol}(T_1) - E_{mol}(T_2)/(2N_L m)$. A relativistically determined Doppler shift of this kind occurs in principle even when the temperatures of the source and the absorber are the same, if the compounds studied have different bonding strengths and hence have different internal energies at the same temperature. Relativistic line shifts are generally small compared to the normally observed isomeric shifts. For example, in the 14.4-keV transition in ^{57}Fe, a temperature difference of 100 °C corresponds to a relativistic line shift which is about an order of magnitude smaller than the isomeric shift between two typical high-spin compounds of Fe^{II} and Fe^{III}. The contribution of the relativistic line shift to the total line shift need therefore only be taken into account in extreme cases, say the case of a large temperature difference or of very different bonding strengths of the test substances used.

4. Electric Quadrupole Splitting of the Gamma Lines

In addition to the isomeric shifts, electric quadrupole splitting of the gamma lines can provide independent information concerning the nature of the chemical bonding. Such quadrupole splitting occurs if at least one of the nuclear states participating in a gamma transition has a nuclear spin $> \frac{1}{2}$ and if at the same time the environment of the nucleus exhibits a symmetry lower than cubic. The component q_{ii} of the tensor of the electric field gradient is given by

$$q_{ii} = (1 - \gamma_\infty) q_{ii}(\text{lattice}) + (1 - R_Q) q_{ii}(\text{ion}).$$

Here the contributions q_{ii} (lattice) due to the surrounding lattice ions and the contribution q_{ii} (ion) due to the valence electrons are each multiplied by Sternheimer factors, which describe an induced charge polarization of the electrons in closed shells. Table 4 contains the relative contributions of q_{ii} (ion) for p- and d orbitals.

Table 4. Electric field gradients for p- and d orbitals.

Orbital	$q_{zz}/\langle 1\ r^3\rangle_{nl}$	$\eta = (q_{xx} - q_{yy})/q_{zz}$
p_x	+2/5	0
p_y	+2/5	0
p_z	−4/5	0
$d_{x^2-y^2}$	+4/7	0
d_{z^2}	−4/7	0
d_{xy}	+4/7	0
d_{xz}	−2/7	+3
d_{yz}	−2/7	−3

In many cases in compounds of the transition elements both nd- and (n+1)p orbitals make direct contributions to the electric field gradient. The lattice component of the field gradient q_{ii} is then generally small compared to that of the valence electrons. This latter contribution depends on the degree of overlap of the partially filled molecular orbitals and the ligand orbitals, and is thus influenced by the degree of covalence of the bond. In addition, however, a contribution from the formally closed electron shells of the metal ion to the field gradient at the nucleus is possible if these shells have sufficient overlap with the ligand orbitals. The perturbation of mainly closed p shells caused by such overlapping—essentially an orthogonalization effect—can lead to substantial quadrupole splitting insofar as closed p shells exhibit particularly large values of the $\langle r^{-3}\rangle$ radial integral which determines the quadrupole splitting.

Calculations by *Sawatzki et al.*[25] for ^{27}Al in Al_2O_3 showed that there the effect of overlapping with closed shells makes the predominant contribution to the electric field gradient. In a way these discussions represent a parallel case to the calculations made by *Šimánek et al.*[11, 12], which demonstrated the significance of the overlap effect for isomeric shifts.

The qualitative magnitude of quadrupole splitting can often be derived from the symmetry of the particular orbitals. Thus, the 3d shell of iron in the high-spin Fe^{III} complexes has a spherical symmetry and the result may be a smaller field gradient q_{ii} (lattice) originating in the ligands. Conversely, in the analogous case of Fe^{II} complexes a highly nonspherical symmetry exists, which typically gives rise to large quadrupole splitting. In the low-spin compounds of iron, as is to be expected, the Fe^{II} complexes exhibit a very small and the Fe^{III} a somewhat larger quadrupole splitting.

By way of illustration, Figure 9 shows for complexes of mono- and divalent gold, a correlation between the quadrupole splitting and the isomeric shift. Such a correlation is understandable if we again start from the assumption of a synergic coupling of σ- and π-bonds. The increase of the isomeric shift with increasing rank of the ligand in the spectrochemical series corresponds to a transfer of s electrons due to strengthened σ_s bonding. This increase must necessarily go together with an intensification of σ_d bonding whereby the quadrupole interaction is directly influenced. However, this argument has only a qualitative character, and it is not, for example, in any way possible to conclude that a linear relation exists between the isomeric shift and quadrupole interaction, since even with proportionality of the s- and d contributions in the σ-bonds, the electron transfers always affect the isomeric shift and the quadrupole splitting to a different degree. Direct proportionality between the two quantities measured can perhaps be assumed for small transfers.

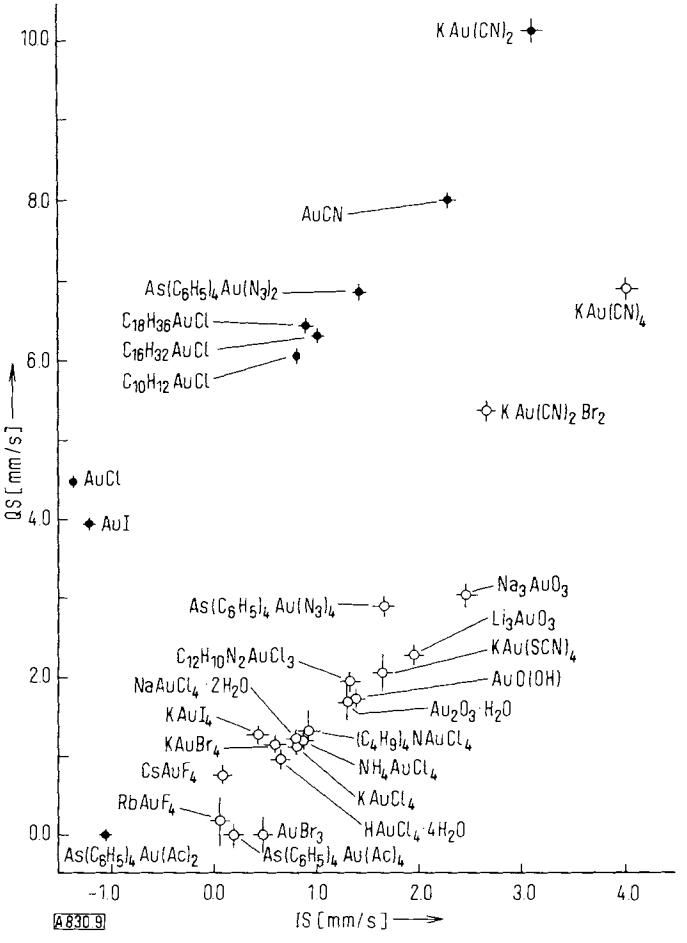


Fig. 9. Correlation between quadrupole splitting QS and isomeric shift IS for compounds of Au^{I}(●) and Au^{III}(○); after [20].

In principle, the sign of the electric field gradient can be taken from the difference in the intensity of the components of the split hyperfine spectrum. However, this method fails for nuclear transitions of the type $I=\frac{1}{2}\leftrightarrow I=\frac{1}{2}$, as for example in the 14.4-keV transition in ^{57}Fe. Here, in polycrystalline substances with more or less isotropic bonding forces, all that is observed as a result of quadrupole interaction is two gamma lines of equal intensity. Determination of the sign of the electric field gradient in this case requires either the use of single crystals or splitting of the nuclear level by means of strong external magnetic fields.

5. Final Remarks

To sum up, it can be said that the method of gamma resonance spectroscopy is capable in a unique manner of yielding information concerning the nature of the chemical bond. Measurements of isomeric shifts can be used directly for the classification of chemical valence states. At the present stage of development, however, the interpretation of these measurements is first and foremost of a very qualitative nature. So far there are no reliable experimental or theoretical methods of determining the relation between the isomeric shift and the electron density at the nucleus. In other words, the problem of calibration of the isomeric shifts still awaits a satisfactory solution. A closely associated problem is that in most cases it has not, so far, been possible to resolve the indirect contribution of the screening electrons from the direct contribution of the s electrons. For a solution of this problem, direct determination of the effective charges of the bound metal ions would above all be of great interest. Unfortunately knowledge of the molecular orbital energies yields this information only very indirectly. High-pressure experiments should in future assume increasing importance for detailed interpretation of isomeric shift data. Systematic comparisons with force constants and with bond lengths and angles—in many cases still unknown—are further possible aids to interpretation. Notwithstanding the often qualitative nature of its statements, gamma resonance spectroscopy has in a few years substantially contributed to our understanding of chemical bonding.

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Methods and Applications of Nuclear Magnetic Double Resonance

By Wolfgang von Philipsborn[*]

In double resonance spectra, transitions between energy levels of a nuclear spin system are measured in the presence of two (or more) oscillating magnetic fields. Experiments of this nature form the basis of what is nowadays one of the most important techniques of NMR spectroscopy. Depending on the method selected, they can be used to unravel complex spectra, to measure hidden or weak resonances, or to determine the relative signs of coupling constants, as well as in stereochemical or kinetic studies. This wide and steadily growing range of applications of double resonance is described with the aid of specific examples.

1. Introduction

NMR spectroscopy is nowadays an essential part of molecular spectroscopy and an indispensable aid in the investigation of the structures of organic and inorganic compounds. Several progress reports on various aspects of the field have appeared in this journal[1-6]. Particularly great progress has been made in recent years in the development and application of double and multiple resonance methods. An effort is therefore made below to describe the methods that are of most interest to chemists, and to demonstrate their use in spectral analysis and for the solution of structural problems. As the literature is extremely abundant, a comprehensive review is impossible here, and the examples were therefore chosen for their illustrative character.

2. Phenomenology and Instrumental Principles

In double resonance experiments, transitions between energy levels of a nuclear spin system in a polarizing static magnetic field H_0 are measured in the presence of two oscillating magnetic fields H_1 and H_2. H_1 is used to observe the resonance of one type of nucleus, and H_2 for the perturbation of a second type of nucleus. The method is based on a proposal made by *Bloch* in 1954, and was successfully realized in the very same year[7]. This first reported experiment was concerned with the determination of the Larmor frequency ($\omega = \gamma H_0$) of ^{13}C in $^{13}CH_3I$; the procedure used

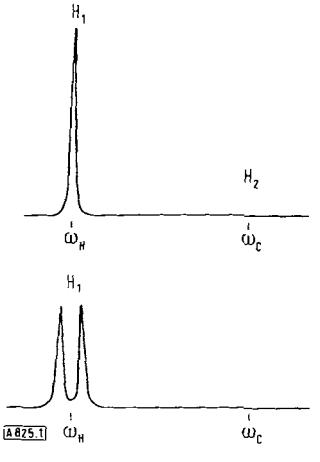


Fig. 1. Schematic illustration of the proton spectrum of $^{13}CH_3I$ (bottom) and *Royden*'s ^1H-{^{13}C} double resonance experiment [7]. Observing field H_1, perturbing field H_2.

was to look for the frequency ω_2 of the perturbing field H_2 that simplifies the proton doublet observed with H_1 to an optimal singlet (Fig. 1). The experiment is thus also

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the simplest case of spin decoupling, since the strong perturbation of the ^{13}C nuclei leads to a breakdown of proton-carbon spin coupling. However, double resonance and spin decoupling are not synonymous, since decoupling effects occur only under certain conditions.

In view of the large number of double resonance experiments known, some classification is necessary. First of all, one distinguishes between *homo*nuclear and *hetero*nuclear experiments, according to whether the nuclear spins in question belong to nuclei of the same type or of different types. This affects the experimental conditions, inasmuch as a second radio frequency can be used for H_2 in the heteronuclear case, whereas in the homonuclear case the second frequency is produced mostly by audio modulation of the spectrometer frequency. The technique of heteronuclear double resonance has been described in two reviews[8, 9]. A comprehensive description of the theory and practice of double resonance with special reference to homonuclear experiments has been published by *Hoffman* and *Forsén*[10]. Since the present article is concerned mainly with the phenomenology and application of double resonance, the reader is referred to the literature for a more profound theoretical study[8, 10].

The experimental methods can best be further classified according to the energy of the perturbing field. The energy γH_2[Hz] ($\gamma = \gamma/2\pi$; γ = gyromagnetic ratio of the nuclei irradiated by H_2; H_2 = amplitude of one of the rotating components of the perturbing rf-field) may be compared here with the nuclear spin interaction $J_{NN'}$ [Hz], the line width $\Delta\nu_{1/2}$ [Hz], or the reciprocal relaxation times $1/T_1$ and $1/T_2$ [Hz]. As the amplitude of the perturbing field decreases, it is possible to distinguish the following cases, where A is the nucleus under observation and X is the perturbed nucleus in any spin system:

Amplitude of the perturbing field [Hz]	Effect on the observed A resonance	Terminology
$\gamma H_2 \gg n \cdot J_{AX}$ (n depends on the nature and number of equivalent X nuclei	Reduction of the number of resonance lines	Spin decoupling
$\gamma H_2 \approx J_{AX}$	Reduction of the number of resonance lines by selective irradiation of the X resonance	Selective spin decoupling
$\gamma H_2 \approx 1/T_2 \approx \Delta\nu_{1/2}$	Additional splitting by submultiplet formation	Spin tickling
$\gamma^2 H_2^2 (T_1 T_2)_X \approx 1$	Changes in the relative intensities of the multiplet lines	Generalized Overhauser effect [a]

[a] Cf. [10] and Section 3.4.

The various double resonance experiments yield different kinds of information, and are illustrated in Section 3 with the aid of some typical examples. The following abbreviation is commonly used for the formal description of such experiments: A-{X} denotes an experiment in which the X resonance in an AX system is totally or partly irradiated by H_2, whereas the A resonance is observed by means of H_1. This can be achieved under various conditions, which determine the appearance of a double resonance spectrum. Since there are five experimental parameters, *i.e.* H_1, ω_1; H_2, ω_2, and H_0, and since ω_1 and ω_2 are related to H_0 by the Larmor conditions for A and X, at least one of the quantities H_0, ω_1, and ω_2 must be varied to enable a double resonance spectrum to be recorded.

The following measuring techniques are distinguished:

1. Variation of field "field sweep":	$\omega_i - \omega_2 = \text{const.}$, $H_0 \pm \Delta H$ variable, *i.e.* the X spectrum is scanned with $\omega_2(H_2)$, while A is scanned with $\omega_1(H_1)$.
2. Variation of frequency "frequency sweep ω_1":	$\omega_2/H_2 = \text{const.}$, $\omega_1 \pm \Delta\omega$ variable; the additional irradiation is fixed for X, whereas $\omega_1(H_1)$ sweeps over the entire A spectrum.
3. Variation of frequency "frequency sweep ω_2": (INDOR [a])	$\omega_1/H_1 = \text{const.}$, $\omega_2 \pm \Delta\omega$ variable; the same line in the A spectrum is always observed, whereas the perturbing field H_2 scans the resonance lines of X.

[a] INDOR = abbreviation for "internuclear double resonance".

In contrast with normal "single resonance" spectra, field-sweep and frequency-sweep double resonance spectra differ from one another. The field-sweep method can be readily used in the homonuclear case when ω_1 and ω_2 are produced by audio modulation of the transmitter frequency ω_0. It is particularly suitable for spin decoupling, and is historically the older technique. However, the number of experiments required for the decoupling of the A nuclei from several nuclei with different chemicals shifts (*e.g.* {X} {Y} ...) is obviously equal to the number of different nuclei. If $\omega_A - \omega_X \gg 2\pi J_{AX}$ (and this is so in first-order spectra), the difference in the modulation frequencies $\omega_1 - \omega_2$ corresponds to the relative chemical shift of A and X, $\omega_A - \omega_X$. It follows therefore that spin decoupling can also be used to determine the (relative) chemical shift of the X nucleus if this resonance is hidden under the resonances of other nuclei. In a frequency-sweep experiment, one of the two fields, H_1 or H_2, must be accurately fixed at a certain point in the spectrum (at ω_1 or ω_2); this is facilitated by field frequency stabilization of the spectrometer. If the perturbing field H_2 is fixed at the resonance of a nucleus which is coupled to several partners the coupling with all the partners can be eliminated in one experiment. The techniques most commonly used at present are 2 and 3.

Another important factor is whether the magnetic fields H_1 and H_2 are stationary or transient, *i.e.* whether their application is of short duration. An additional parameter in double resonance experiments is therefore the rate of change of frequency for the observing and perturbing fields (sweep rate). This is particularly important in experiments in which intensity changes are observed as a result of changes in the populations of the energy levels (Overhauser effects). Time-dependent intensity changes of this nature in double resonance experiments are discussed in Section 3.5.

3. The Methods and their Uses

The double resonance methods indicated in Section 2 can be applied to a wide variety of problems, as is clear from the following survey:

Method	Use
Noise decoupling (broad-band decoupling) heteronuclear	Simplification and sensitivity enhancement in spectra of nuclei that give low intensities, *e.g.* ^{13}C-{^{1}H} and also ^{19}F-{^{1}H} experiments.
Spin decoupling heteronuclear and homonuclear	Structure elucidation by definite identification of spin-coupled nuclei and simplification of complicated multiplets; detection of hidden resonances; simplification of spectra of multispin systems to obtain preliminary sets of parameters for computer calculations.
Selective spin decoupling	Assignment problems within complex and overlapping multiplets; determination of the relative signs of scalar nuclear spin couplings.
Spin tickling	Accurate measurement of the frequencies of hidden resonance lines; assignments in strongly coupled spin systems; identification of subspectra; determination of the relative signs of coupling constants; construction of energy level diagrams.
Overhauser effects	
(a) Generalized OE (spin pumping) (GOE)	Accurate measurement of the frequencies of hidden resonance lines by INDOR spectroscopy, determination of proton sequences, elucidation of structures; determination of relative signs of coupling constants; construction of energy level diagrams; indirect determination of the chemical shifts of nuclei giving low intensities, *e.g.* ^{13}C, ^{14}N, ^{31}P, by heteronuclear INDOR spectroscopy.
(b) Classical *inter*molecular internuclear OE	Investigation of relaxation processes in liquids and gases.
(c) *Intra*molecular internuclear OE (NOE)	Semiquantitative determination of internuclear distances, solution of stereochemical problems; measurement of relaxation and correlation times; intensity enhancement of weak nuclear resonances, *e.g.* ^{13}C.
Transient double resonance experiments	Kinetic studies on spin systems with chemical exchange, determination of exchange rates and spin-lattice relaxation times.

Their value will now be demonstrated with the aid of specific problems. The space devoted to the various examples does not necessarily reflect their relative importance, which should in fact be greatest for the less well known, more recent methods.

3.1. Spin Decoupling

This is the oldest method. The disappearance of spin-spin coupling in an A-{X} system can be best understood if one considers the double resonance experiment in a rotating system of coordinates ("rotating frame"). For a system of Cartesian coordinates rotating about the direction of the static magnetic field H_0 (z axis) with a frequency ω_2, the time-dependent perturbation caused by H_2 becomes a stationary perturbation in the x direction. H_0 then appears to be reduced to $H'_0 = H_0 - \omega_2/\gamma$, and the X nucleus perturbed by H_2 is exposed to an effective field $\vec{H}'_0 + \vec{H}_2$. If ω_2 corresponds to the resonance frequency of the X nucleus, this leads to $H'_0 = 0$ and to an effective quantization of X in the direction of $H_2(x)$, *i.e.* perpendicular to H_0, the z direction, in which the A nucleus observed with H_1 ($H_1 \ll H_2$) and coupled with X is quantized. Since the scalar nuclear spin coupling is given by the product $J_{AX} \cdot \vec{I}_A \cdot \vec{I}_X$, orthogonal quantization of A and X results in a collapse of the spin coupling.

The analytical importance of spin decoupling for the unraveling of complex NMR spectra was recognized very early, and experiments with this aim were carried out first on heteronuclear[7, 8, 11, 12] and later on homonuclear systems[13]. Heteronuclear experiments of the type H-{X} and X-{H} can greatly simplify the spectra of protons in compounds containing ^{2}H, ^{11}B, ^{14}N, ^{19}F, or ^{31}P and facilitate the interpretation of the spectra of the corresponding hetero nuclei[9]. It is essential in experiments of this type that the transmitting coil of the spectrometer be able to accommodate both Larmor frequencies and that it be tuned accordingly or that a second transmitting coil be incorporated[14]; the second radio frequency may be advantageously supplied by a frequency generator.

An important and frequent application is the decoupling of the protons from deuterium in specifically deuterated organic compounds. The proton resonances in such cases are greatly broadened as a result of ^{1}H, ^{2}H spin coupling and deuterium quadrupole relaxation effects (Fig. 2), However, for kinetic studies by NMR line shape analysis the line width should be as small as possible. An example is provided by the determination of the free enthalpy of activation ($\Delta G^{\neq} = 8.1$ kcal/mole) for the ring inversion of cyclooctane on the basis of the ^{1}H resonance of $C_8D_{15}H$ with ^{1}H-{^{2}H} decoupling[15]. Similarly, $\Delta G^{\neq} = 10.2$ kcal/mole was found for the ring inversion of cyclohexane from the temperature-dependent ^{1}H spectra of $C_6D_{11}H$[16a–c].

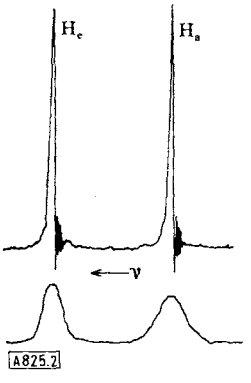


Fig. 2. Proton spectrum of [D_{11}]-cyclohexane at −100 °C (bottom) and with decoupling from the deuterium nuclei (top); $\nu_e - \nu_a = 28.7$ Hz (60 MHz) [16c].

The advantage of this double resonance technique is that the kinetics in complex spin systems such as in C_8H_{16} and in C_6H_{12} can be reduced to a simple two-center exchange in $C_8D_{15}H$ and $C_6D_{11}H$ respectively (Fig. 2), with the result that more accurate thermodynamic activation parameters can be obtained. The vicinal proton coupling constants in 2,2,3,3,4,4,5,5-octadeuteriocyclohexane have also been determined from the ^{1}H-{^{2}H} double resonance spectrum[17]. Heteronuclear ^{1}H-{^{14}N} and ^{1}H-{^{11}B} decoupling have proved excellently suited for the analysis

of nitrogen heterocycles, such as pyrrole[18] and pyridine[19] and of boranes[20]. ^{11}B-{^1H} decoupling has been used for the analysis of the ^{11}B spectra of carboranes[21]. For further examples and instrumental details the reader is referred to [8, 9].

decoupling of the ^1H resonance, the carbon spectra can be greatly simplified and the signal/noise ratio for this low-intensity nucleus can be improved (cf. also Section 3.4.3). Figure 4 shows the application of this double resonance process to the ^{13}C spectrum of pyridine that contains

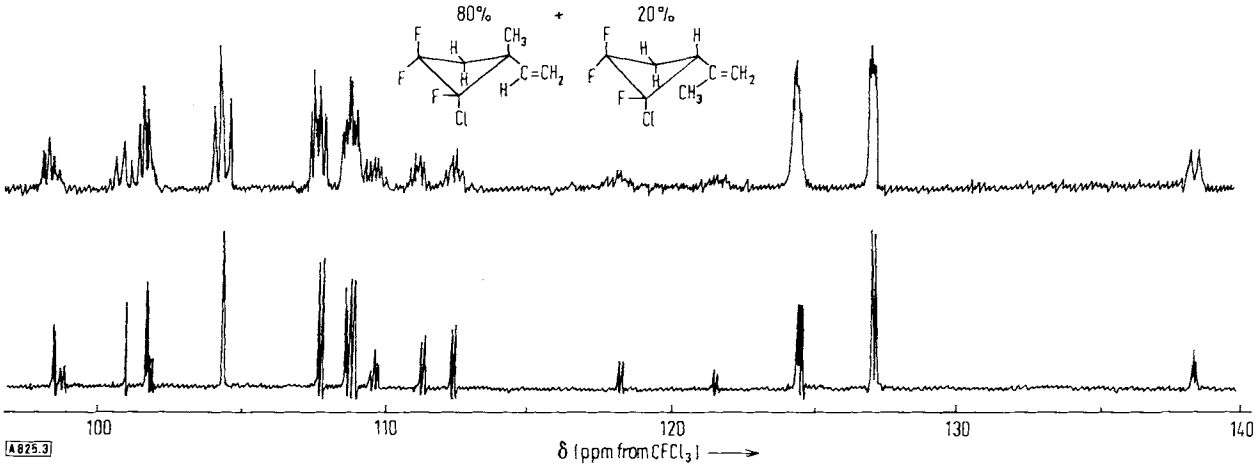


Fig. 3. ^{19}F spectra of a mixture of two substituted cyclobutanes, which are themselves mixtures of *cis-trans* isomers; top: normal spectrum, bottom: proton noise-decoupled spectrum [22].

Difficulties are encountered in the use of the decoupling technique when the resonances of the types of nuclei to be irradiated extend over a large frequency range. This is so in ^1H-{^{19}F} and ^{19}F-{^1H} experiments because of the magnitude of the proton-fluorine coupling. A similar problem arises when one wishes to measure the ^{13}C resonances of a molecule with complete decoupling of all protons. The required frequency range (a few hundred to one thousand Hz) of the perturbing field H_2 is achieved by a method known as *noise decoupling*[22]. In this method, the perturbing field H_2 can be applied pseudo-randomly over a wide frequency range (*e.g.* 1000 Hz) with the aid

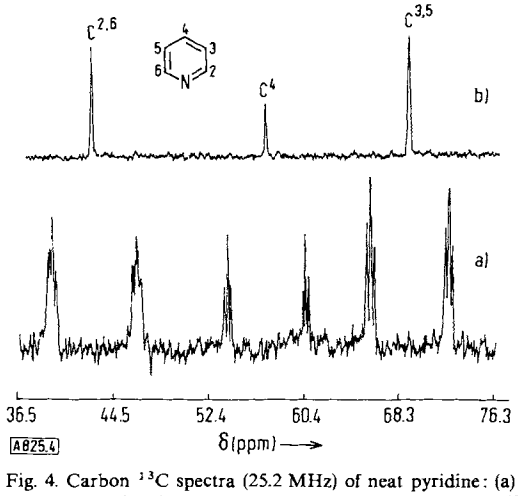


Fig. 4. Carbon ^{13}C spectra (25.2 MHz) of neat pyridine: (a) 16 computer-accumulated spectral scans; (b) 1 scan, measured with {^1H} noise decoupling; chemical shifts relative to CS_2 (Varian Assoc.).

of a shift pulse generator, so that all the nuclei are covered in a very short time. The first examples were described by *Ernst* for the ^1H,^{19}F double resonance (Fig. 3); however, the most important use nowadays is in the measurement of the ^{13}C resonance of organic compounds. By complete

the carbon isotope in natural abundance (1.1%). The importance of such ^{13}C-{^1H} double resonance spectra for the elucidation of structures becomes obvious when one considers the noise-decoupled carbon spectrum of 4-allyl-4-methyl-2,5-cyclohexadien-1-one (Fig. 5)[23].

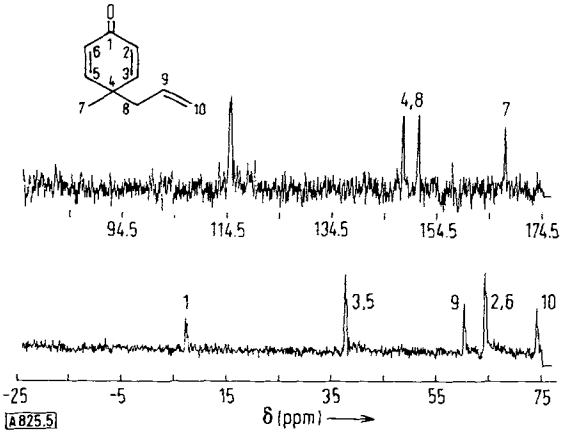


Fig. 5. Carbon ^{13}C spectrum (25.2 MHz) of 4-allyl-4-methyl-2,5-cyclohexadien-1-one in $CHCl_3$, {^1H} noise decoupling; chemical shifts relative to CS_2 [$\delta(CHCl_3) = 115.0$ ppm].

The conditions for homonuclear (*e.g.* ^1H, ^1H) experiments are nowadays satisfied by the equipment of standard spectrometers, and have been described in detail[8-10]. We shall therefore confine ourselves here to a brief description of the difference between homonuclear field-sweep and frequency-sweep double resonance spectra. Figure 6 shows the 100 MHz spectrum of the alkaloid fruticosine, the structure of which was verified by double resonance experiments[24]. The region between 2.4 and 4.8 ppm contains the signals of twelve protons, six of which are assigned to two separate AMX systems, H-C(4)-C(3)HOH and $H_2C(10)$-C(11)H. Six separate irradiations are required here, since only one spin coupling is eliminated in each

experiment. This disadvantage disappears in the frequency-sweep method.

The irradiation of the H^5 resonance in mannosan triacetate (Fig. 7) simplifies the signals of all the protons coupled with this nucleus, *i.e.* H^2, H^3, H^4, $H^{6'}$ and $H^{6''}$[25]. This

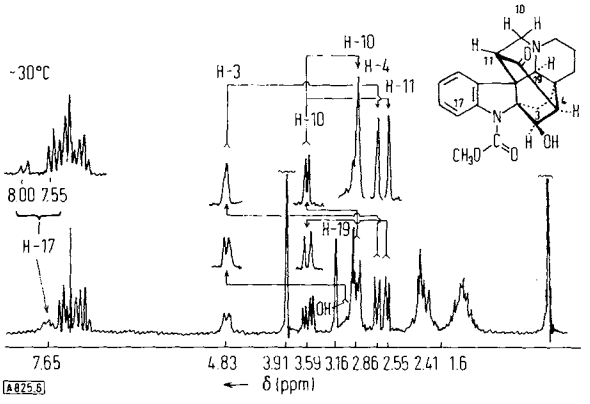


Fig. 6. ^1H spectrum of the alkaloid fruticosine (100 MHz) and field-sweep double resonance spectra; irradiation position ↑, observation position ↓ [24].

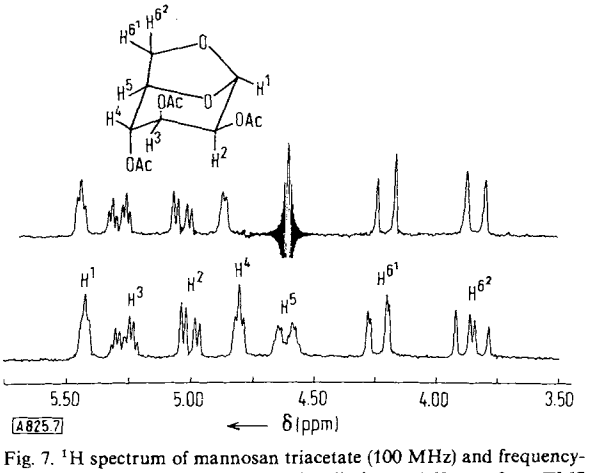


Fig. 7. ^1H spectrum of mannosan triacetate (100 MHz) and frequency-sweep double resonance spectrum; irradiation at 4.62 ppm from TMS [25].

example can also serve for the demonstration of the frequency shifts that occur in double resonance spectra. In the double resonance spectrum of Figure 7, the signals of all the decoupled protons are displaced to different frequencies in relation to their original position, the shift being greatest in the neighborhood of $\omega_2(H_2)$. The irradiation of the X resonance with H_2 causes a shift in the Larmor frequency of the nucleus A under observation as a result of the Bloch-Siegert effect[26]:

$$\omega_A \rightarrow \omega_A + \frac{\gamma^2 H_2^2}{2(\omega_A - \omega_2)} \approx \omega_A + \frac{\gamma^2 H_2^2}{2(\omega_A - \omega_X)} \quad (1)$$

In experiments in which $\omega_A - \omega_X \gg 2\pi J_{AX}$ is not satisfied, moreover, the value of ω_2 for optimum decoupling differs from the chemical shift of the X nucleus ω_X:

$$\omega_2 \rightarrow \omega_X + \frac{\gamma^2 H_2^2}{\omega_A - \omega_X} \quad (2)$$

Both correction terms are easily explained[27]. In frequency-sweep experiments, eq. (2) must be taken into account in fixing ω_2. In the field-sweep technique, the variable is $\omega_1 - \omega_2$, so that eq. (1) and (2) enter into the correction formula:

$$(\omega_1 - \omega_2) = (\omega_A - \omega_X) - \frac{\gamma^2 H_2^2}{2(\omega_A - \omega_X)} \quad (3)$$

The frequencies of the lines observed in double resonance spectra can thus be regarded only as approximations to the values for the unperturbed spin system. This is important when spin decoupling is used to simplify complicated systems in accurate analyses. Nevertheless, an important application of this double resonance method is the determination of preliminary sets of parameters for iterative computer calculations (cf. Fig. 16).

3.2. Selective Spin Decoupling

The spin decoupling method cannot be applied to strongly coupled spin systems or to systems with overlapping multiplets, since perturbation of the lines of neighboring nuclei is unavoidable. However, double resonance spectra that are easy to interpret and that can be used for assignment purposes are obtainable by reduction of the amplitude of the perturbing field H_2 so that only part (an accurately defined part) of a multiplet is perturbed. This "selective" decoupling method can be best illustrated for a three-spin AMX system ($I = \frac{1}{2}$) (Fig. 8).

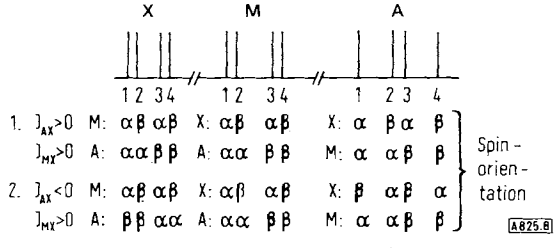


Fig. 8. Schematic three-spin AMX spectrum ($I = \frac{1}{2}$) and spin orientations of the nuclei for the various lines with like and unlike signs of J_{AX} and J_{MX}.

Irradiation on the right-hand M doublet produced by J_{AX} simplifies only one of the corresponding X doublets to a singlet. This is understandable if one considers that the two M doublets (M_1, M_2) and (M_3, M_4) are produced by different molecules, which differ in the spin state (α or β) of the A nucleus. The same is true of the two X doublets. Irradiation of the M resonance in one type of molecule can decouple only the X nuclei in the same type of molecule. The information obtained from selective decoupling of this nature is the same as from a total decoupling experiment, and it can be used *e.g.* in questions of assignment in the elucidation of structures.

The question which of the two X doublets is decoupled by irradiation of M_3 and M_4 depends only on the relative signs of J_{AX} and J_{MX} (Fig. 8). This double resonance (DR) method is thus suitable for the determination of signs of coupling constants, and was first applied to the diethylthallium ion $(C_2H_5)_2Tl^+$[28], furan-α-carboxylic acid[29], and fluorinated ethanes[30]. Figure 9 shows the M and X part of the 100 MHz spectrum of the vinyl protons of

furan-α-carboxylic acid and a selective decoupling experiment carried out by frequency sweep[*]. It shows that $J_{AX}=J_{4,5}$ and $J_{AM}=J_{3,4}$ are of like sign (cf. Fig. 8).

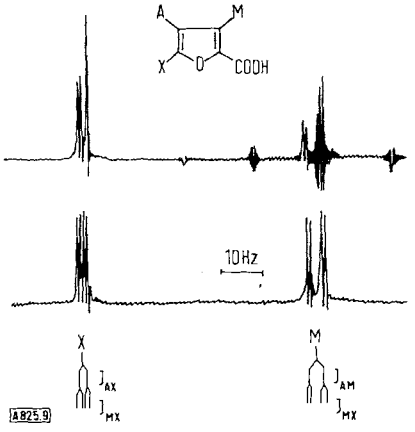


Fig. 9. ^{1}H spectrum of the M and X protons of furan-α-carboxylic acid (bottom) and selective decoupling experiment by irradiation of the two highest-field lines of M.

[*] The original experiment by *Freeman* and *Whiffen* [29] was carried out under field-sweep conditions.

Similar DR experiments can be carried out in heteronuclear systems. Figures 10a and 10b show the 100 MHz proton spectrum and the 94.1 MHz fluorine spectrum of 2-fluoro-4-allyl-4-methyl-2,5-cyclohexadien-6-one. Irradiation of the two lowest-field lines of H-5, *i.e.* elimination of $J_{5,F}$, simplifies the left-hand branch of the fluorine spectrum from a septet to a sextet (Fig. 10c). It follows that the signs of $J_{3,5}$, $J_{5,6}$, $J_{3,F}$, and $J_{6,F}$ are the same[31].

It is even possible in certain cases to determine the magnitudes and relative signs of unresolved spin couplings. It can be seen from Figure 11 that elimination of J_{AX} in the X part of an AMX spectrum by selective irradiation of suitable A transitions produces an unsymmetrical X triplet, from which $|J_{MX}|=|(\Delta_1-\Delta_2)|/2$ and the relative signs of J_{MX} and J_{AM} can be found even when J_{MX} is very small and not resolved in the original spectrum. Irradiation of the four lowest-field lines of H-5 (Fig. 10d) changes the two doublets of H-3 ($J_{3,6}$ not resolved) into two triplets that are unsymmetrical toward the right, from which one obtains $J_{3,6}\approx 0.1_5$ Hz, with *opposite* signs for $J_{5,6}$ and $J_{3,6}$. Since $J_{5,6}$, as a vicinal H,H coupling, has a positive sign[32], $J_{3,6}$ must have a negative sign.

The relative signs of the nuclear spin coupling constants can be determined by various DR experiments (cf. the survey

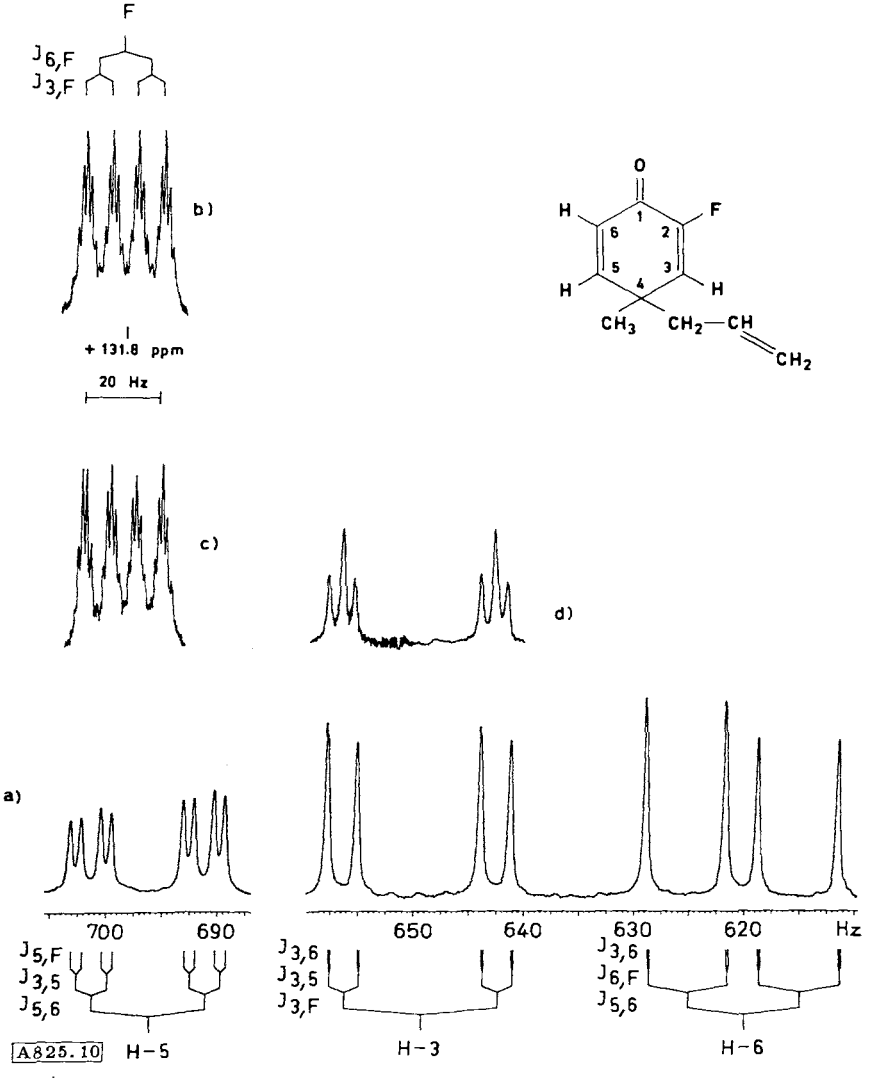


Fig. 10. ^{1}H spectrum (a) and ^{19}F spectrum (b) of 2-fluoro-4-allyl-4-methyl-2,5-cyclohexadien-1-one; (c) selective ^{19}F-{^{1}H} decoupling experiment; (d) ^{1}H-{^{1}H} decoupling to eliminate $J_{3,5}$ [31], cf. Fig. 11.

on p. 474). Together with the magnitude of J and the chemical shift, it is a further source of information on which structural and theoretical conclusions can be based. Since the relative signs of most of the typical H,H couplings are now known, their determination can be of decisive value in the investigation of unknown structures, particularly in

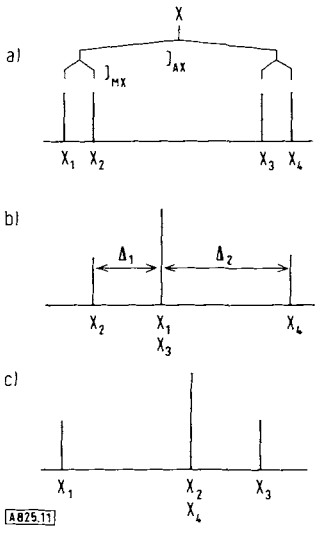
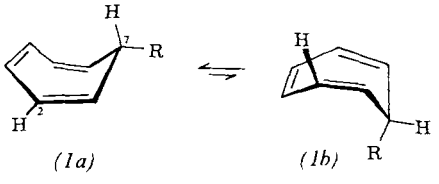


Fig. 11. Schematic representation of the X part of an AMX spectrum: (a) normal spectrum, (b) and (c) double resonance spectra with selective irradiation of the A part and elimination of J_{AX}.

stereochemical problems, in cases where $|J|$ alone does not allow any definite conclusions. For example, the preferred conformation *(1a)* of 7-substituted cycloheptatrienes was deduced from the (negative) sign of the allylic coupling $J_{2,7}$[33].

There is no doubt that too little attention has been given to the significance of the relative signs of coupling constants for structural problems.

On the other hand, these experimentally determined signs have proved to be important test quantities for quantum-chemical calculations of the scalar nuclear spin coupling.



(1a) *(1b)*

This spin coupling takes place *via* the bonding electrons, is an intrinsic phenomenon of the molecule, and is therefore independent of nuclear magnetic resonance. It is thus of direct interest to the theory of molecular structure. Calculations have been carried out for σ and particularly for π electron systems[34]. A comparison of the results with experimental coupling constants and their relative signs enables interesting conclusions to be drawn regarding the validity of the underlying theories, the mechanisms of scalar spin coupling, and the nature of the chemical bonding in σ systems[35], π systems[36], and organometallic compounds[37].

3.3. Spin Tickling

If the amplitude of H_2 is further reduced and γH_2 reaches the order of magnitude of the line width $\Delta\nu_{1/2}$ or of the reciprocal transverse relaxation time T_2^{-1}, the perturbation is confined to one transition and the associated energy levels. Under these double resonance conditions, spectral lines that have an energy level in common with the perturbed transition will be split into submultiplets[38]. The magnitude of the doublet splitting observed in nondegenerate systems[*] is proportional to the amplitude of H_2 and the square root of the intensity of the irradiated line. Lines that are regressively[40] connected to the perturbed transition normally give well resolved doublets, whereas progressively connected lines give poorly resolved (broad) doublets. The tickling experiment can be best illustrated by the schematic spectrum and energy-level diagram of an

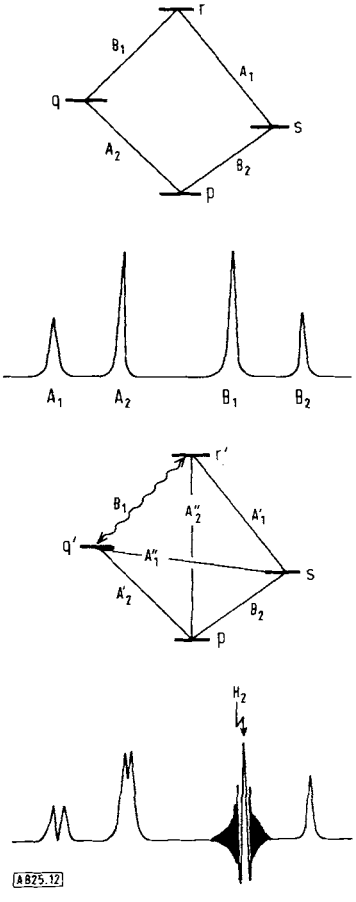


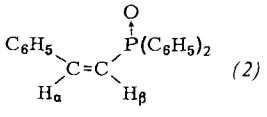
Fig. 12. Schematic representation of an AB spectrum and energy-level diagram (top); tickling experiment for the B_1 transition (bottom) and energy-level diagram with transitions in the rotating frame.

AB system (Fig. 12). *Freeman* and *Anderson*[38a] have developed a theory that has been extended by *Lippmaa et al.*[38b], and which can explain the phenomena observed in tickling experiments. It is again advantageous to choose a system of Cartesian coordinates that rotates around the direction of the magnetic field H_0 (z axis) with a frequency ω_2 ("rotating frame"). If the transition B_1 (q↔r) in Figure 12 is perturbed by H_2, the line A_2 that is progressively connect-

[*] Splitting into several lines is observed in degenerate systems [27]; for spin tickling with nuclei having $I=1$, cf. [39].

ed to B_1 splits into a doublet, since the eigenstate q appears in the two new states q′ and r′ as a result of mixing of the states q and r. From the standpoint of the rotating system of coordinates, the two A_2 lines can then be assigned to the transitions p↔q′ and p↔r′. The same is true of the transition A_1 that is regressively connected to B_1. If ω_2 is exactly the same as ω_{qr} (B_1), the two doublet lines A_2' and A_2'' have the same intensity and appear at distances of $\pm\frac{1}{2}\gamma_B H_2$ from A_2. On the other hand, if ω_2 differs somewhat from ω_{qr}, an unsymmetrical doublet is observed. Since the additional irradiation with H_2 is fixed on a certain line (± 0.1 Hz) in tickling experiments, a field frequency stabilized spectrometer is required for this method. Corresponding experiments have been carried out under field-sweep conditions, and give different results[38a].

This double resonance method is excellently suited for the determination of the exact frequencies of hidden or overlapping resonance lines, since the doublet splitting depends very sensitively on the perturbing frequency ω_2[41]. A



(2)

typical application in the elucidation of structures is shown in Figure 13. The problem here is to determine the configuration of the olefinic double bond in styryldiphenylphosphane oxide *(2)* from the ^{1}H-NMR spectrum.

is to be expected for the vicinal *cis* and *trans* proton-phosphorus couplings. However, J_{HP}^{vic} can be found only from the hidden H_α multiplet, the lines of which can be determined very accurately by tickling experiments (Fig. 13). The coupling constant $J_{HP}^{vic}=40.3$ Hz obtained from the four lines is greater than $J_{HP}^{trans}=30.2$ Hz in trivinylphosphane, whereas J_{HP}^{cis} in this compound is only 13.5 Hz. This result proves the *cis* configuration of the protons in the phosphane oxide *(2)*[43].

The spin tickling technique can also be used for the determination of the chemical shifts of low-intensity, heavy nuclei. The chemical shifts of ^{129}Xe in xenon fluorides[44] and of ^{103}Rh in triphenylphosphane-rhodium complexes[45] have been measured in this way.

However, this method of establishing the positions of hidden or weak resonances is very laborious and time-consuming if a very large frequency range must be scanned in very small intervals (≈ 0.2 Hz) with ω_2. In such cases the INDOR technique (ω_2 sweep) is superior to spin tickling. This technique is discussed in Section 3.4.2.

Another important use of spin tickling is in the determination of the relative signs of coupling constants. Figure 14 shows the energy-level diagrams for a three-spin system with the four possible combinations of signs for J_{AB}, J_{AC}, and J_{BC}. Reversal of the sign of a coupling constant leads to interchange of the transitions of the two nuclei in question in the corresponding rectangles. This changes the connection of the energy levels and hence the tickling pat-

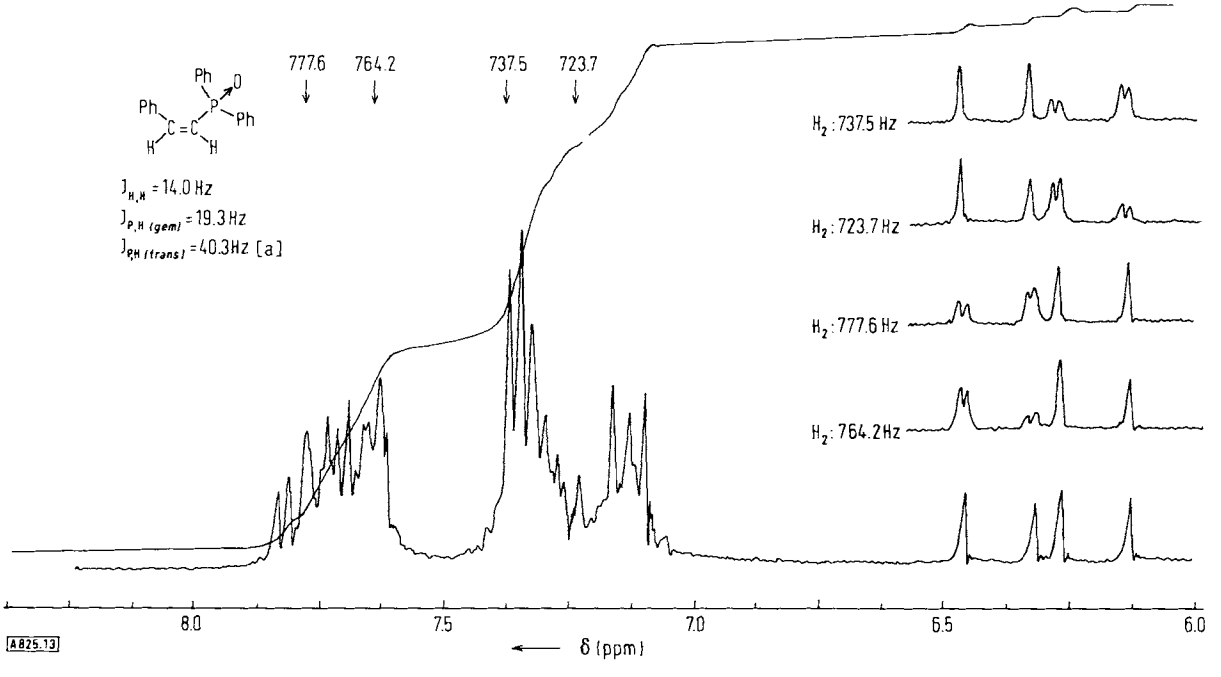
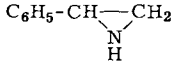


Fig. 13. ^{1}H spectrum of styryltriphenylphosphane oxide *(2)* (100 MHz) and tickling experiments to determine the frequencies of the four hidden lines of H_α [43].

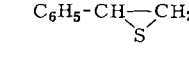
[a] Calculated from spin tickling data.

Whereas the β vinyl proton is visible, the α vinyl proton is completely masked by the phenyl resonances. Thus only $J_{HH}^{vic}=14.0$ Hz can be found from the ^{1}H spectrum, while J_{HP}^{vic} cannot. The magnitude of J_{HH}^{vic} does not allow a definite distinction between the *cis* and *trans* arrangements of the vinyl protons[42] On the other hand, a greater difference

tern. It has been shown in this way[46] that the coupling constants of the geminal methylene protons in the α,β-epimino



(3)



(4)

derivative *(3)* and in the α,β-epithio derivative *(4)* of styrene have opposite signs.

Figure 15 illustrates the spectra of *(3)* and *(4)* and a comparison of the double resonance spectra on irradiation of the A_1 transition. Whereas the lines B_1, B_3 and C_1, C_3 have

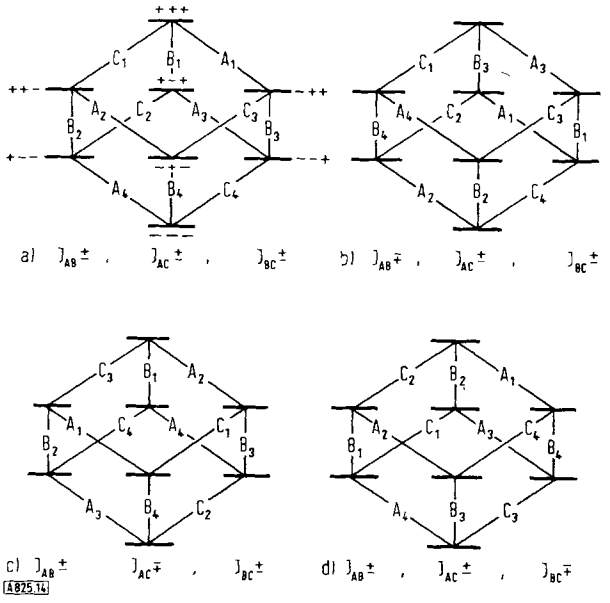
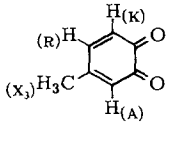


Fig. 14. Energy-level diagrams and transitions for a three-spin system ($\nu_A \gg \nu_B \gg \nu_C$) with the four combinations of signs of the coupling constants, $|J_{AB}| > |J_{AC}| > |J_{BC}|$.

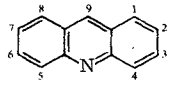
energy levels in common with A_1 in the imine *(3)*, the transitions that share energy levels with A_1 in the case of the sulfide *(4)* are B_2, B_4 and C_2, C_4. This is in agreement with the energy-level diagrams (a) for the imine and (d) for the sulfide, *i.e.* the coupling constants $J_{BC}=J_{gem}$ have opposite signs in the two styrene derivatives. Since the signs of all three couplings are the same for *(3)* and vicinal H,H coupling constants are absolutely positive, the geminal coupling in *(4)* must have a negative sign, as is observed for cyclopropanes. The change in the sign of J_{gem} in three-membered rings is a particularly interesting case of the structure dependence of the signs of nuclear spin coupling constants.

Tickling experiments are particularly suitable for multiple resonance studies. Thus the same sign was found for the three coupling constants of the vinyl protons in 4-methyl-



(5)

o-benzoquinone *(5)* in one experiment[47]. The six-spin system ($AKRX_3$) formed by the three ring protons and the methyl group was first simplified to an AKR system by



$J_{1,9}$ and $J_{3,9}$: negative[*]
$J_{2,9}$ and $J_{4,9}$: positive

(6)

[*] Based on a positive sign for J_{ortho}.

strong irradiation at the methyl resonance, and one R line was simultaneously perturbed by a weak field in a triple resonance experiment (Fig. 16). The alternance of the signs of the long-range H,H spin coupling constants in acridine *(6)* have been demonstrated similarly by a triple resonance analysis of 1-methylacridine and 2-methylacridine[48].

This result confirms theoretical predictions concerning the relative signs of proton-proton coupling in aromatic systems[36].

Since tickling experiments not only give the relative signs of the coupling constants but also the nature of the connection (progressive or regressive) of the observed transition with the irradiated transition, double resonance experiments of this type are the best method for the construction

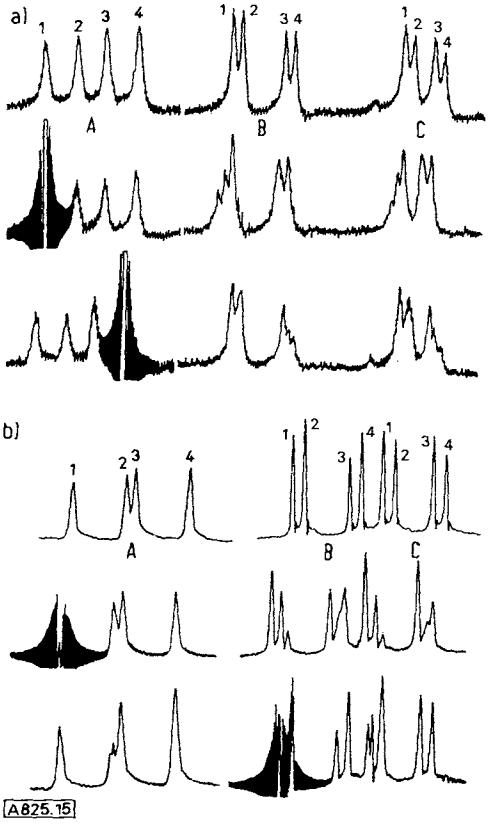


Fig. 15. ^1H spectra and tickling experiments on the side-chain protons of (a) styrenimine *(3)* and (b) styrene sulfide *(4)* [46].

of complete energy level diagrams[38a]. Other important uses occur in the identification of the components of subspectra in complicated multispin systems and in the analysis of the spectra of oriented molecules[49].

The splitting into submultiplets of the lines connected to the perturbed transition is always accompanied by a change in the intensities of these lines. The population changes in the levels of the perturbed transition increase the intensity of the progressive transitions and reduce that of the regressive transitions[27]. Intensity changes of this nature always also occur in the double resonance experiments discussed so far, since a weaker field H_2 is sufficient for this. The condition for these pure population changes is $\gamma^2 H_2^2 T_1 T_2 \geq 1$, and the effect on the intensities is known as the generalized Overhauser effect (GOE)[10]. A wide range of applications can be found for such effects.

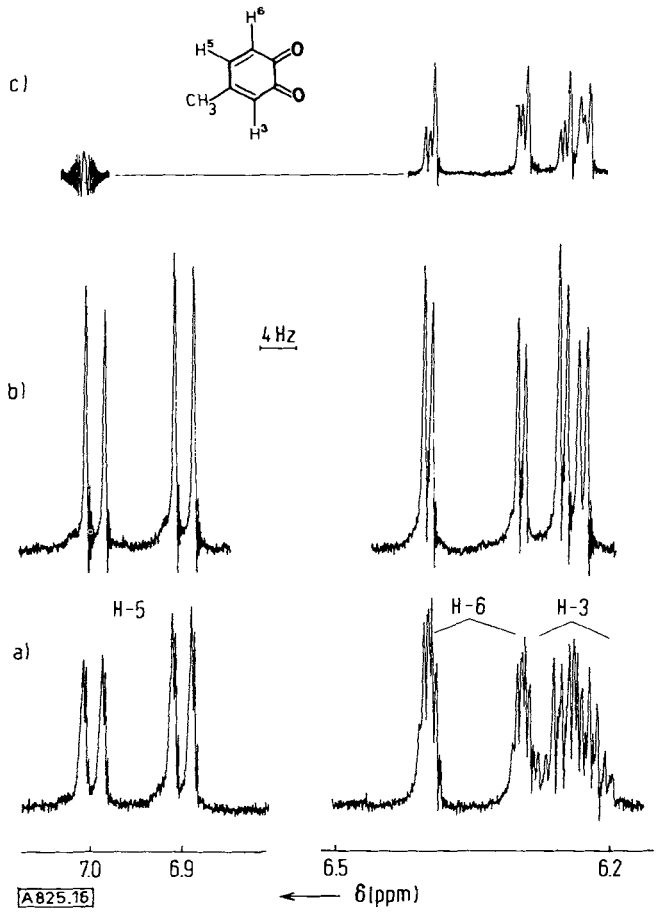


Fig. 16. ^1H spectra of 4-methyl-*o*-benzoquinone *(5)* [47]; (a) normal spectrum ($CDCl_3$, 100 MHz); (b) double resonance spectrum with irradiation of the methyl protons; (c) triple resonance spectrum with irradiation of the methyl protons and tickling of the lowest-field line (700.5 Hz) of H-5.

3.4. Overhauser Effects

In this section we shall discuss double resonance experiments that are based essentially on population changes in the energy levels and which cause corresponding intensity changes in the spectra. The Overhauser effect is really the polarization of nuclei as a result of the saturation of the electron spins in metals[50, 51]. However, it has become common practice to apply the same name to corresponding *inter*molecular and *intra*molecular internuclear polarization effects based on the relaxation mechanism (dipolar coupling). On the other hand, intensity changes observed in double resonance for connected transitions in spin systems with exclusively scalar coupling are collectively known as the "generalized Overhauser effect"[10]. Since this effect follows directly on the last section, it is convenient to discuss it here.

3.4.1. Generalized Overhauser Effect (GOE)

The first effect of this type was observed by *Anderson* and *Freeman*[27] in tickling experiments. These authors perturbed one line in the X_3 part of the AX_3 spectrum of acetaldehyde and found a change in the relative intensities in the quartet of the A part. These intensity changes occur because the irradiation with H_2 causes a change in the populations of certain energy levels as compared with the thermal equilibrium populations. A quantitative treatment[52a] of the processes requires a precise knowledge of the (thermal) relaxation mechanisms and times, which would have to be determined for each spin system. The reader is referred to a detailed review[52b] for a discussion of the physical processes involved. A qualitative description of the situation that is adequate for practical purposes has been presented by *Kaiser*[53], who also described the first practical applications of this effect. Under certain conditions regarding the relaxation times, the following general rules can be established (cf. Fig. 17):

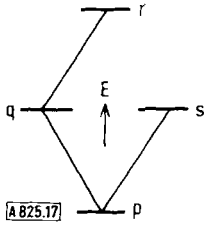


Fig. 17. Connection of transitions in the energy level diagram: q↔r is progressive and p↔s regressive with respect to p↔q.

1. Irradiation of a line (transition) influences only lines that have an energy level in common with it.

2. Irradiation of a nondegenerate line reduces the intensity of a regressive line and increases the intensity of a progressive line.

This Overhauser effect may also be regarded as a consequence of "spin pumping". The information obtained from such experiments is fundamentally the same as that obtained from spin tickling, *i.e.* the relative signs of coupling constants, the assignment of transitions to certain energy levels, and the location of hidden or weak resonances. This will be illustrated here by the normal spectrum and the double resonance spectrum of *m*-dinitrobenzene. This compound gives an AB_2C spectrum (Fig. 18), which can be described approximately as a first order spectrum[53]. Very weak irradiation of the transition 23 increases the intensities of lines 8 and 10 and decreases those of lines 7 and 13. This can be understood from the energy level diagram (Fig. 19), and the signs of all four coupling constants of the aromatic protons are found to be the same. Other examples are the analysis of the AX_3 system of acetaldehyde and the ABM_3X system of *trans*-crotonaldehyde[53], and the determination of signs for 2,6-dinitrobenzaldehyde[54].

The intensity changes, which are sometimes very small, must be detected by comparison with unperturbed lines. However, measurement by the INDOR sweep technique is recommended, since signal intensities are also influenced by instrumental effects (*e.g.* momentary changes in the field then be used above all to find the positions of hidden or homogeneity)[53]. The generalized Overhauser effect can weak resonance lines.

3.4.2. INDOR Spectroscopy

In the INDOR sweep technique, as was mentioned in Section 2, the frequency ω_2 of the perturbing field H_2 is

varied over the entire spectral range, while the observation field H_1 is used for the measurement of a monitor line (ω_1). This method was first described and used by *Baker*[55]. The characteristic feature of such an experiment is that a change in the intensity of the monitor line occurs whenever ω_2 coincides with the frequency of a line that has an energy level in common with the monitor transition at ω_1. This intensity change is plotted as a function of ω_2, and the corresponding INDOR signals are positive for progressive transitions and negative for regressive transitions. The relative intensity changes due to the Overhauser effect are thus recorded as more easily recognizable, absolutely positive or absolutely negative signals[*].

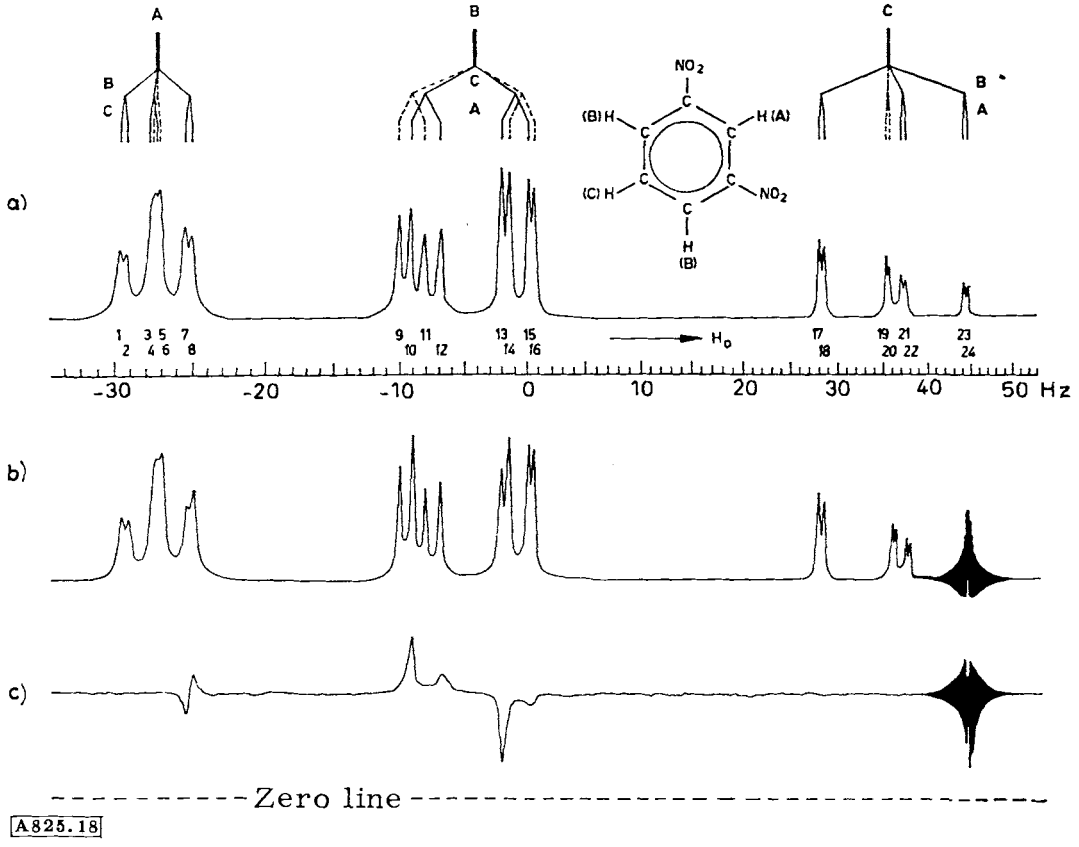


Fig. 18. (a) ^1H spectrum (AB_2C) of *m*-dinitrobenzene (56.4 MHz). The differences between the full and the dotted lines in the splitting diagram would disappear in the limiting AM_2X case. (b) Double resonance spectrum with weak irradiation of line 23; lines 7 and 13 ↓ (regressive), lines 8 and 10 ↑ (progressive). (c) Double resonance INDOR spectrum (ω_2 sweep) with line 23 as the monitor line: positive INDOR signals at the frequencies of lines 8 and 10, negative INDOR signals at the frequencies of lines 7 and 13. Weak INDOR signals also appear at the frequencies of lines 12 and 15 because of partial overlapping of lines 23 and 24. Cf. [53, 10] and energy level diagram in Fig. 19.

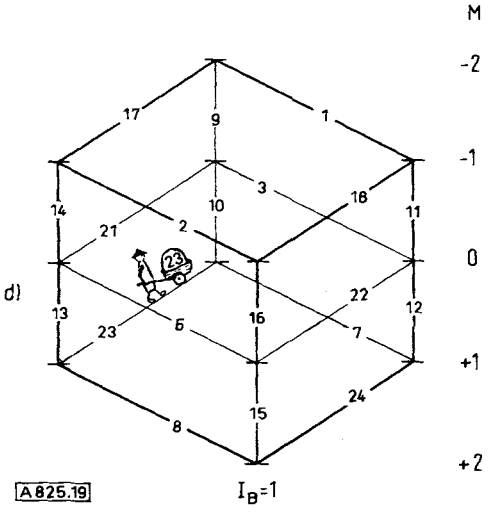


Fig. 19. Energy level diagram of the symmetrical states ($I_B = 1$) for the four-spin system of *m*-dinitrobenzene with an illustration of spin pumping on irradiation of line 23 (Fig. 18) [10, 53].

INDOR experiments have been carried out both on heteronuclear and on homonuclear systems. However, applications so far have not been very numerous. According to a review by *Kowalewski*[56], they are concerned either with the determination of the chemical shifts of nuclei other than protons or with the determination of signs of coupling constants. Heteronuclear ^1H-{^{31}P} INDOR experiments have been successfully used for the analysis of mixtures of organophosphorus compounds[57]. In the homonuclear version, the method is also excellently suited for the accurate determination of the frequencies of hidden resonances of a proton that exhibits scalar coupling with the monitor proton. This double resonance technique has great potential here for the elucidation of the structures of complex molecules[58].

The INDOR principle is illustrated in Figure 20 for a three-spin AMX system. If a nondegenerate monitor line is chosen (A_1), two INDOR signals appear for each proton

[*] The use of higher amplitudes of H_2 leads to tickling effects that result in an increase of the negative INDOR signals and a decrease of the positive signals.

coupled with A. However, if $J_{AX}=0$ and the monitor line is degenerate (A_1, A_2), four signals are obtained for M, but none for X. To obtain the entire INDOR signal of the M nucleus, two experiments with different A lines are necessary in the A———X case (Fig. 20b), whereas one is sufficient in the A—M—X case (Fig. 20d). If the M and X signals are hidden in a practical case, therefore, not only can the line frequencies of M and X be determined with great accuracy (±0.1 Hz), but the coupling constants of these nuclei can also be found.

The intensive application of the INDOR technique allows the complete determination of the structure of a thermal dimerization product *(8)* of 11,13-dioxo-12-methyl-12-aza[4.4.3]propellane *(7)*[58].

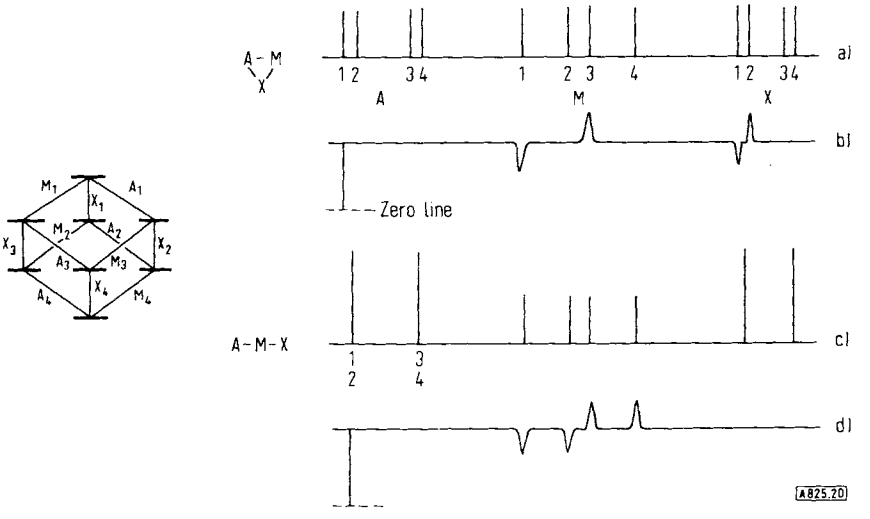


Fig. 20. Schematic spectra of an AMX system and energy-level diagram: (a) normal spectrum, $J_{AM}>J_{MX}>J_{AX}>0$; (b) INDOR spectrum for case (a), monitor transition A_1; (c) normal spectrum, $J_{AM}>J_{MX}>0$, $J_{AX}=0$; (d) INDOR spectrum for case (c), monitor transitions A_1, A_2.

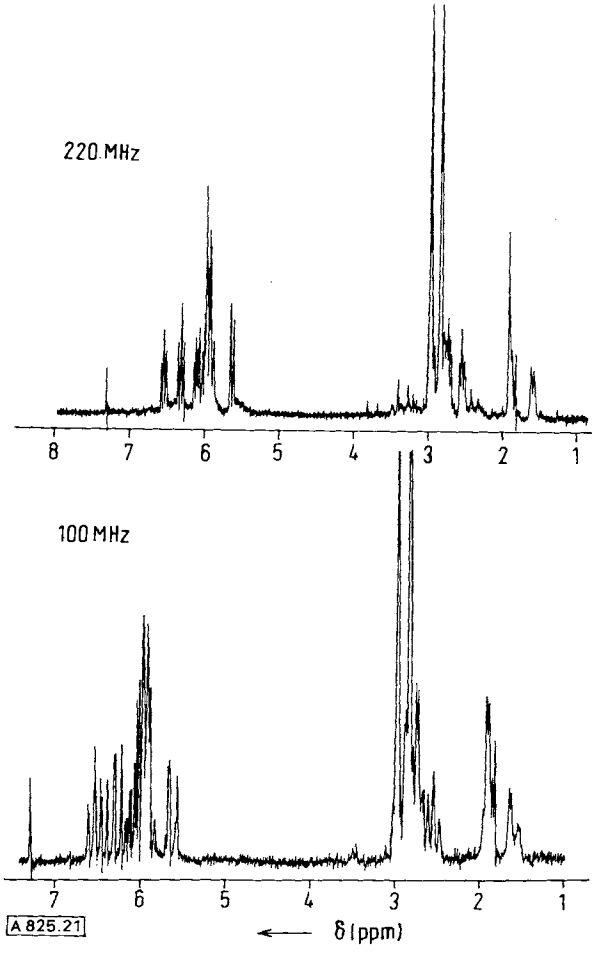
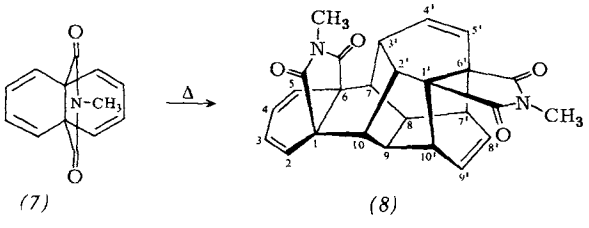


Fig. 21. Proton spectra of the propellane dimer *(8)* at 100 MHz and 220 MHz ($CDCl_3$) [58].

The 100 MHz and 220 MHz spectra of the dimer (Fig. 21) are extremely complex, and conventional double resonance methods cannot be applied. Only four of the sixteen ring protons are resolved in the spectrum. Of these, the two



(7) *(8)*

vinyl protons H-4′ and H-8′ in particular may be used as monitor protons. Figure 22 shows the determination of the four lines of H-5′, while Figure 23a illustrates the detection of ten lines of the protons H-9′, H-7′, and H-10′, all of which are coupled with H-8′, but are hidden in the spectrum. INDOR lines can also be used as monitor lines for consecutive INDOR experiments (Fig. 23b), and this allows the elucidation of proton sequences. The technique has been applied for the same molecule, and Figure 24 illustrates that starting with only three observed protons, eleven of the twelve protons of the skeleton are detected in this way. The use of the INDOR method is not restricted to first order spectra. Thus the chemical shift and coupling parameters of the ABCX system of the four protons of the dimer *(8)* have been established by determination of 32 INDOR frequencies and subsequent evaluation with the aid of an iterative computer program. Other uses of $^1H,^1H$ INDOR in structural studies have recently been published[59-61]. This technique has also proved useful in the

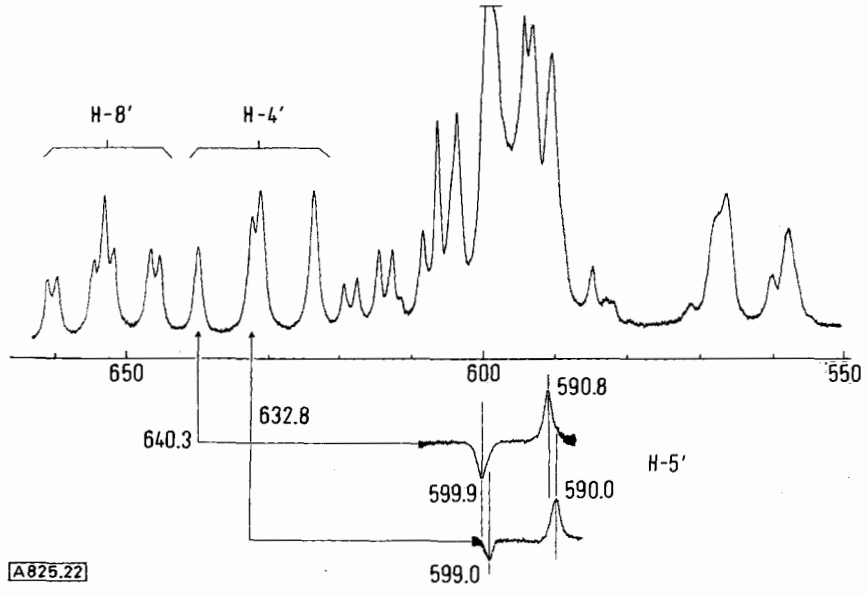


Fig. 22. 100 MHz spectrum of the vinyl region of the dimer *(8)* and INDOR experiments for the determination of the four hidden lines of H-5'; frequencies in Hz [58].

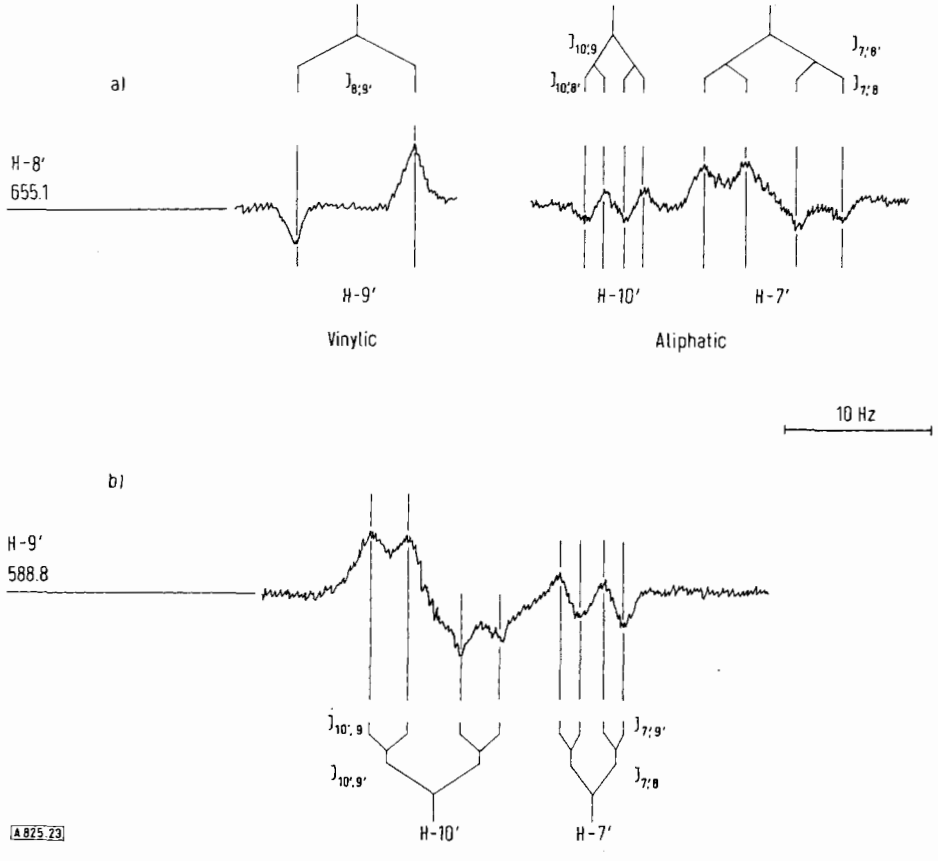


Fig. 23. (a) INDOR spectra of H-9', H-7', and H-10' of the dimer *(8)*, measured with a monitor line (655.1 Hz) of H-8'. (b) Consecutive INDOR spectra of H-7' and H-10', measured with an INDOR line (588.8 Hz) of H-9' as the monitor frequency [58].

analysis of the ^{19}F spectra of *threo/erythro* mixtures[62]. It may be expected that INDOR spectroscopy will find wide use in the elucidation of structures.

The first applications, however, were in heteronuclear double resonance, and made use of the high sensitivity of the ^{1}H or ^{19}F nuclei for the measurement of the resonances of nuclei whose direct measurement is difficult because of low natural abundance and small gyromagnetic constants (*i.e.* poor sensitivity) and because of long relaxation times[55]. This group includes the nuclei ^{13}C, ^{14}N, ^{29}Si, and ^{31}P. The measurement of the carbon resonance in organic compounds is particularly facilitated in this way[41, 63, 63a, 64]. However, methods of this type have now

been displaced by Fourier spectroscopy, combined with noise decoupling (see Sections 3.1 and 3.4.3).

Whereas the experiments described so far proceed under quasi-stationary conditions, and the new populations for the energy levels in question are established under the influence of relaxation processes, INDOR experiments can also be carried out under conditions that correspond to a

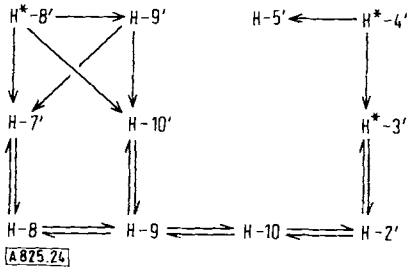


Fig. 24. Proton sequence for the dimeric propellane *(8)*, deduced from INDOR experiments. The arrows point from the monitor proton to the INDOR proton. Protons that can also be observed directly in the spectrum are marked with an asterisk.

fast adiabatic passage across the {X} resonance. The "transient nutations"[65] (Torrey oscillations[66]) that then occur in the monitor resonance, which is also saturated, provide information similar to that obtainable from normal INDOR signals (see Section 3.5.3).

3.4.3. Internuclear Overhauser Effects (NOE)

Apart from the chemical shifts and coupling constants, the relaxation times T_1 and T_2 are the most important parameters in NMR spectroscopy, since they determine the excess of nuclei that remain in the lower energy level when the spin system absorbs energy from the rf field H_1. For protons,

$$\frac{n^s}{n^0} = (1+\gamma^2 H_1^2 T_1 T_2)^{-1} \qquad (4)$$

where n^s is the population excess in the lower level in the presence of H_1, and n^0 is that in the absence of H_1. Since the signal intensity is proportional to the population excess n^s, the intensity of an NMR signal can be increased by reducing T_1 or T_2 by means of external factors.

One of the mechanisms that allow proton relaxation in liquids is the magnetic dipole-dipole interaction between nuclei in different molecules, *e.g.* as a substrate-substrate or substrate-medium interaction. The movement of the molecules produces fluctuating dipole fields, with the result that transitions are induced between Zeeman levels

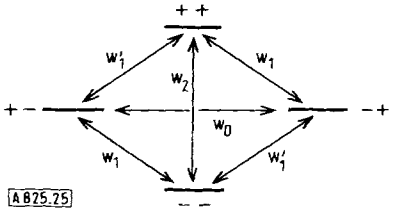


Fig. 25. Energy-level diagram and transition probabilities for a two-spin system with dipole-dipole interaction.

of the nuclei[67]. We now consider a pair of nuclear spins (I,S) that exhibits no scalar coupling and for which the only relaxation path available is the internuclear dipole-dipole mechanism. The transition probabilities corresponding to the change in the quantum number m ($\Delta m = 0, \pm 1, \pm 2$) are denoted by w_0, w_1, and w_2 (Fig. 25). If one of the nuclear resonances (S) is saturated by a strong perturbing field H_2 (*i.e.* $n_S^s = 0$), the change in the longitudinal magnetization of I is given[68] by

$$M_I - M_I^0 = \left(\frac{w_2 - w_0}{w_0 + 2w_1 + w_2}\right) M_S^0 \left(\frac{\gamma_S}{\gamma_I}\right) = (w_2 - w_0)\, T_{1I} M_S^0 \left(\frac{\gamma_S}{\gamma_I}\right) \qquad (5)$$

For the homonuclear case (*e.g.* protons), $M_I^0 = M_S^0$ and $\gamma_S = \gamma_I$, and we obtain

$$\frac{M_I}{M_I^0} = 1 + \left(\frac{w_2 - w_0}{w_0 + 2w_1 + w_2}\right) = 1 + (w_2 - w_0) T_{1I} \qquad (6)$$

M_I^0 = magnetization of I in the absence of H_2;
M_I = magnetization of I on saturation of S by H_2.

Calculations based on a pure dipole-dipole interaction between I and S have shown that $(w_2 - w_0)/(w_0 + 2w_1 + w_2)$ assumes the value $\frac{1}{2}$, *i.e.* that the maximum increase in the intensity of the I resonance to be expected for protons under these circumstances is 50%. The internuclear Overhauser effect (NOE) was first observed by *Kaiser*[69] for the signal of the chloroform proton in a mixture of chloroform and cyclohexane when the cyclohexane protons were saturated. The relaxation time T_1 of the $CHCl_3$ protons can also be determined here as the time constant of the build-up and breakdown of the additional magnetization, which agrees well with the value obtained from the direct saturation of the $CHCl_3$ resonance. However, the observed increase in intensity was only 34%. This means that the chloroform protons are not relaxed exclusively *via* the cyclohexane protons, but that there are also other relaxation paths (*e.g. via* the paramagnetic oxygen in the solution) that contribute to the total transition probability $(w_2 + 2w_1 + w_0)$ and hence to the effective relaxation time T_1.

$$\frac{1}{T_{1I}} = \frac{1}{T_{1S}} + \frac{1}{T'} \qquad (7)$$

If there is only scalar coupling between I and S, the saturation of S causes more or less saturation also of the I-spins, *i.e.* a decrease in the signal intensity[70]. The two effects may therefore be expected to be superimposed if a chemical bond exists between the nuclear species.

However, the significance of the NOE to structural chemistry, which was recognized by *Anet* and *Bourn*[71], is that it can be observed between protons of the same molecule if these are close together in space. The contribution to the longitudinal relaxation time T_1 of a nucleus I due to *intra*-molecular dipole-dipole relaxation by a second nucleus S is given by

$$\frac{1}{T_{1IS}} = \frac{\hbar^2 \gamma_I^2 \gamma_S^2}{d^6} \tau \qquad (8)$$

where τ is a correlation time for the molecular rotation and d is the internuclear distance between I and S. The intramolecular NOE should therefore depend very critically on the internuclear distance. It was soon found that this effect is suitable for the study of molecular structures, particularly for the solution of stereochemical problems. This can be illustrated by the differentiation between the two isomeric ethylideneazabicyclo[2.2.2]-octanes *(a)* and *(b)* (Fig. 26). The compounds were in a mixture and gave different chemical shifts for the methyl and bridgehead protons. Saturation of one methyl resonance (principal component) increased the intensity of one bridgehead proton signal by 31% and had no effect on the signal of the second bridgehead proton. Irradiation of the methyl resonance of the minor component gave no Overhauser effect, so that the main component must have structure *(a)* and the minor component structure *(b)*[72]. It has not been possible to achieve this differentiation with certainty by any other spectroscopic method.

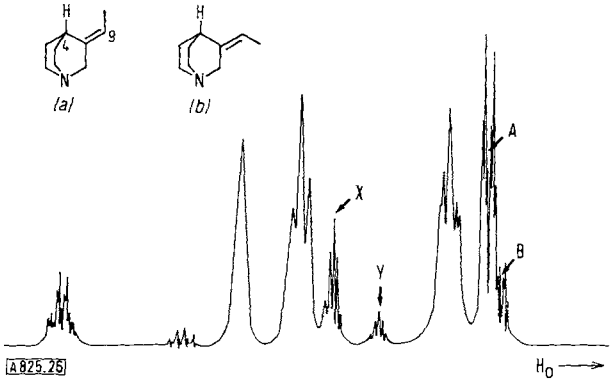


Fig. 26. ^{1}H spectrum of a mixture of the isomeric azabicyclo[2.2.2]-octanes (*a*) and (*b*); A and B correspond to the methyl groups on C-9, and X and Y to the C-4 methine protons. Saturation of the A resonance produces a 31% increase in the intensity of the X resonance and has no effect on Y. Saturation of the B resonance has no effect on the X and Y resonances, *i. e.* A and X may be assigned to the structure (*a*) [72].

Similar investigations have been carried out on innumerable different structures[73], *e. g.* for alkaloids[74, 75], terpenes[76], steroids[77], and penicillin derivatives[78], and the method is extremely elegant for the solution of difficult stereochemical problems. The NOE has been used for the investigation of the preferred conformation of nucleotides with respect to the N-ribose linkage (the *syn-anti* problem)[79]. It must be noted, however, that great care is necessary in the evaluation of NOE data in systems with mobile conformations, since transfer of spin saturation becomes possible if the time constant of the conformational change is smaller than the relaxation time of the nucleus[80]. In such cases it is necessary to use the temperature dependence of the NOE or transient methods. Negative as well as positive NOE values are sometimes observed. It has been shown[75] that alternating signs are to be expected when dipole-dipole interaction is the dominant relaxation mechanism in a series of neighboring protons.

A	B	C	D
saturated	NOE positive	NOE negative	NOE positive

It would be possible in principle to use the NOE for the measurement of relaxation times, correlation times, and interatomic distances. *Bell* and *Saunders*[81] have described a correlation of a large number of NOE values with the internuclear distances d, and have experimentally confirmed the d^6 dependence required by the theory (Fig. 27). Quantitative relaxation studies using the NOE have been carried out on amides by *Brownstein* and *Bystrov*[82].

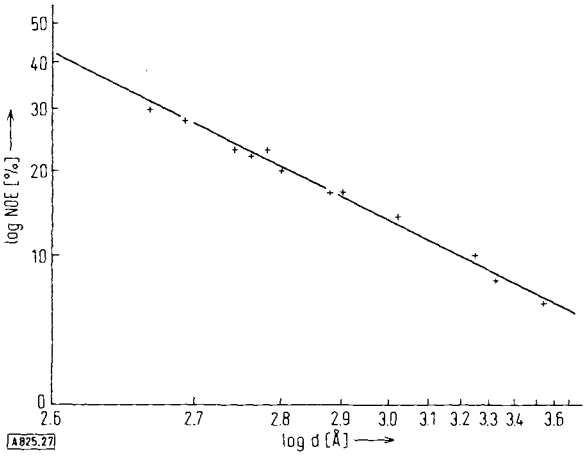


Fig. 27. NOE observed in methyl compounds as a function of the internuclear distance CH_3—H (double logarithmic plot). The straight line has a slope of -6 [81].

Another important application of the Overhauser effect lies in the signal enhancement of low-intensity nuclei. The direct measurement of the ^{13}C carbon resonances is nowadays usually carried out under the conditions of complete decoupling of the carbon nuclei from the protons of the same molecule (noise decoupling; see Section 3.1). Not only is the entire intensity thus concentrated in one line, but this is additionally enhanced by a heteronuclear intramolecular NOE. The factor γ_S/γ_I must be taken into account in eq. (5) for heteronuclear systems, the value of this factor for a $\{^1H\}$-^{13}C system being 3.976. ^{13}C-$\{^1H\}$ noise decoupling thus leads to much greater NOE values than in the homonuclear case. An enhancement of 200% has been observed in the ^{13}C resonance of H—^{13}COOH[83a]. This effect can also be seen in Figure 4, which shows the improvement of the signal/noise ratio in the ^{13}C spectrum of pyridine as a result of the combination of decoupling and the Overhauser effect. Carbon atoms that are not directly bonded to hydrogen atoms give practically no NOE, so that the relative intensities of the ^{13}C resonances often allow the differentiation of tetrasubstituted from monosubstituted, disubstituted, and trisubstituted C atoms. However, the factors that determine the relative intensities of ^{13}C signals are extremely diverse and are the subject of intensive research[83b]. The ^{1}H, ^{13}C spin coupling information is normally lost in noise-decoupled spectra. However, if the perturbing field for the protons is applied for only a short time, one can obtain non-decoupled ^{13}C spectra that are still intensified by the NOE[84]. If the NOE is undesired for quantitative evaluations of ^{13}C spectra it may be eliminated by an addition of paramagnetic compounds[84a].

3.5. Transient Double Resonance Experiments

3.5.1. Double Resonance and Chemical Exchange

The NMR spectra of nuclei that are taking part in a chemical exchange, *e.g.* between the two centers A and B,

$$\underset{T_{1A},\ T_{2A}}{A} \longleftarrow H \longrightarrow \underset{T_{1B},\ T_{2B}}{B}$$
$$\tau_A \qquad\qquad \tau_B$$

are influenced by this exchange if the average residence times in A and B, τ_A and τ_B, are so short that they become comparable with the transverse relaxation times T_{2A} and and T_{2B}. This is the basis of line shape analysis, which allows the study of kinetic processes by means of high-resolution NMR spectroscopy[6]. Since $T_1 > T_2$ in most cases, the range of application of NMR spectroscopy can be extended toward slower reactions by linking τ_A and τ_B with T_{1A} and T_{1B}. *Hoffman* and *Forsén*[85] have developed a double resonance method for this purpose; the method has been applied to proton exchange reactions. When a proton is transferred between the centers A and B, the effective lifetime of a spin state in a given location (*e.g.* H bonded to A) is determined by the new time constant τ_{1A}:

$$\frac{1}{\tau_{1A}} = \frac{1}{T_{1A}} + \frac{1}{\tau_A} \tag{9}$$

The change in the z magnetization of the proton in A is then given[86] by

$$\frac{dM_z^A}{dt} = \left(\frac{M_0^A}{T_{1A}}\right) - \left(\frac{M_z^A}{\tau_{1A}}\right) + \left(\frac{M_z^B}{\tau_B}\right) \tag{10}$$

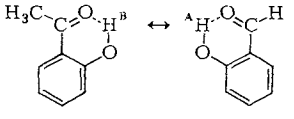
Strong additional irradiation of the proton in B causes saturation of its resonance ($M_z^B = 0$), and solution of eq. (10) then gives

$$M_z^A = M_0^A\left(C \cdot e^{-t/\tau_{1A}} + \frac{\tau_{1A}}{T_{1A}}\right) \tag{11}$$

In the steady state ($t = \infty$), the ratio of the magnetization of H in A with and without double resonance is

$$\frac{M_z^A}{M_0^A} = \frac{\tau_{1A}}{T_{1A}} \tag{12}$$

which is the ratio of the signal intensities of HA. $\tau_{1A} < T_{1A}$, *i.e.* τ_A comparable with T_{1A}, then leads to a decrease in the intensity of HA, which means a transfer of saturation from HB to HA by chemical exchange. The time constant τ_{1A} can be obtained by a semilogarithmic plot of $M_Z^A - M_0^A(\tau_{1A}/T_{1A})$



(10) *(9)*

against t after τ_{1A}/T_{1A} has been found from the stationary double resonance experiment (eq. (12)). Combination with eq. (12) and eq. (9) then gives T_{1A} and τ_A. The time constants τ_{1B}, τ_B, and T_{1B} are obtained in a similar manner from a B-{A} experiment.

This method can be used for the quantitative investigation of the intermolecular exchange of the OH protons in a 5.7:1 mixture of salicylaldehyde *(9)* and 2-hydroxyacetophenone *(10)*[85].

Figure 28 shows the exponential decrease and increase in the OH signal intensity of *(9)* when the strong perturbing field for the OH resonance of *(10)* is switched on and off. The evaluation of the decisive time interval (a few seconds) and the measurement of the intensities of HA without the perturbing field H_2 and after the prolonged action of H_2 (stationary case) gave $\tau_A = 11.53$, $\tau_B = 2.17$, $T_{1A} = 5.43$, and $T_{1B} = 3.70$ s. The time constants τ_{1A} and τ_{1B} are 3.75 and 1.33 s respectively.

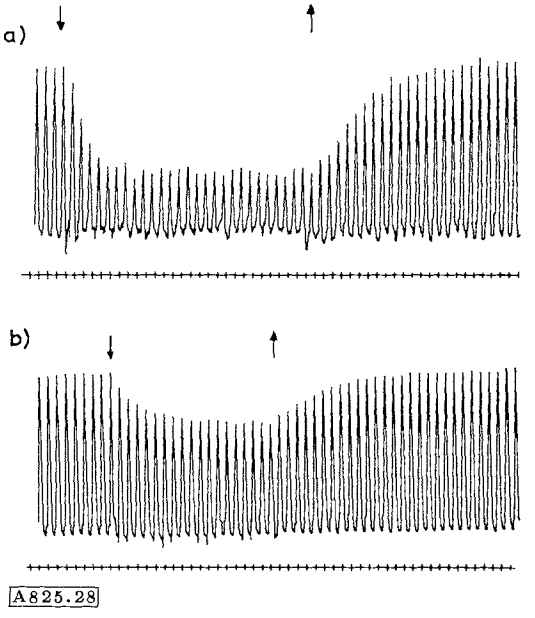
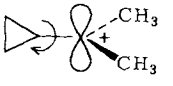


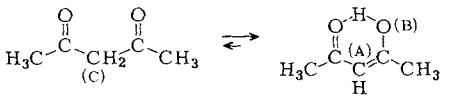
Fig. 28. (a) Decrease and increase in the OH signal intensity of salicylaldehyde *(9)* when the saturation field H_2 for 2-hydroxyacetophenone *(10)* is switched on (↓) and off (↑) in a mixture of the two compounds. (b) Analogous experiment for the OH resonance of *(10)*. The scale interval is one second [92].

Other applications of the relaxation method have now been reported. It was possible in this way to extend the NMR kinetics of the ring inversion in undecadeuteriocyclohexane to the temperature range −97 to −117 °C and τ_A values of 3.8 to 236 s[16c]. The energy barrier for internal rotation in the cyclopropyldimethylcarbonium ion *(11)* has also been determined[87].



(11)

The method can also be extended to exchange processes between three non-equivalent centers. Thus the average residence times of the protons at the oxygen, methylene, and vinyl centers in the keto-enol equilibrium of acetylacetone have been determined in this way[87].



(12a) (12b)

The residence times in this case are again so long ($\tau_A = 14.0$, $\tau_B = 14.2$, $\tau_C = 3.8$ s) that the chemical exchange has no effect on the normal NMR spectrum at room temperature.

The saturation transfer technique can also be used qualitatively to detect the presence of exchange processes. The conformational mobility of [18]-annulene at room temperature was detected in this way, since saturation of the "inner" vinyl protons results in the disappearance of the resonance of the "outer" vinyl protons[88]. The same principle forms the basis of an experiment in which the OH resonance in phenols is detected by irradiation of the water signal and transfer of saturation to the OH protons[89]. The phenomenon can be described in general form in the density-matrix formalism[89a]. In spin systems with scalar coupling, the saturation transferred by chemical exchange is transferred further to adjacent coupled nuclei, *i.e.* a *negative* Overhauser effect (NOE) is observed[88, 90, 91]. This is due to the fact that for scalar coupling, $w_0 > w_2$ in eq. (6), and hence $M_1/M_1^0 < 0$[70].

3.5.2. Transitory Selective Irradiation (TSI)

In the use of the generalized Overhauser effect to deduce the energy-level diagram of a multispin system, the changes in population should preferably be confined to the levels of the irradiated line. Only then do Overhauser effects occur exclusively in "directly connected" lines. In the stationary experiment, the perturbing field H_2 must act for a time T_2^* corresponding to the reciprocal line width of the irradiated transition. The optimum observation time (t) for the intensity changes after H_2 is switched on is

$$T_2^* \ll t \ll T_1$$

where T_1 may be regarded as the shortest reciprocal thermal transition probability T_{pq} (spin-lattice relaxation time). Maximum intensity changes are observed when the perturbing field H_2 traverses the line in an adiabatic fast passage. Such TSI experiments[92] give particularly clear Overhauser effects, since relaxation losses are minimized and population changes occur only in the levels of the perturbed line.

3.5.3. Transient Nutations (Torrey Oscillations)

This double resonance method[65] again allows the construction of the energy-level diagram, *i.e.* the determination of the relative signs of coupling constants. The phenomenological picture is similar to that in INDOR spectra, but the monitor line is also saturated by an intense field H_2. Whenever H_2 meets a line that has an energy level in common with the monitor line, a sudden transfer of population occurs to the common energy level, since the populations of the levels are reversed in the perturbed line[66]. The sudden spin pumping initiates positive or negative "Torrey oscillations" in the monitor resonance, which allow the differentiation of regressive and progressive transitions (Fig. 29)[65]. This technique also allows the detection of weak lines, *e.g.* combination lines, and has been used for the indirect measurement of the ^{13}C resonance[63, 64]. As a transient method, it is less influenced by relaxation effects than normal stationary Overhauser experiments, and gives results similar to those obtained by the TSI technique.

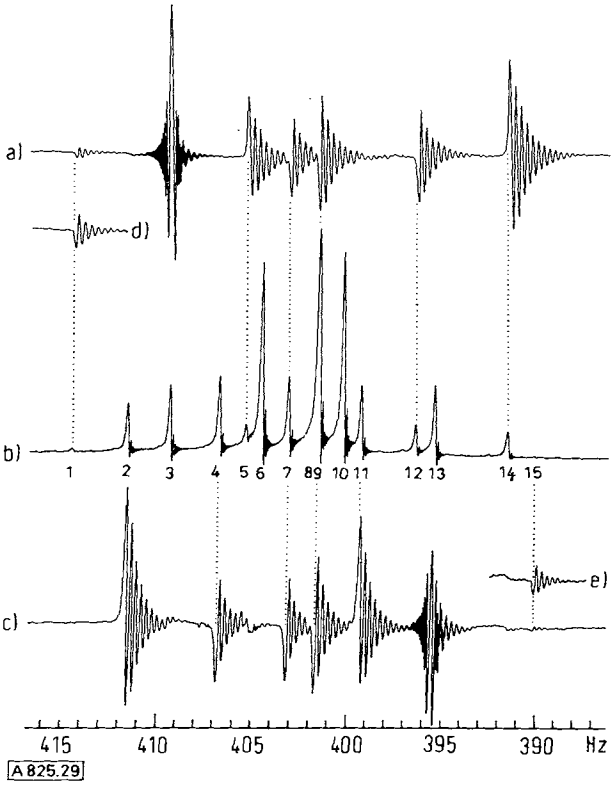


Fig. 29. (b) ^1H spectrum of 2-chlorothiophene (60 MHz) [65]. "Transient nutations" obtained (a) in the monitor line 3 and (c) in the monitor line 13. Signals for which the initial deflection is positive indicate progressive transitions, and negative signals indicate regressive transitions. (d) and (e) illustrate Torrey oscillations that correspond to very weak transitions, and which are obtained by increasing the amplitude of H_2.

3.5.4. Double Resonance and Fourier Transform Spectroscopy

When a nuclear spin system is stimulated by an intense rf pulse of short duration, all the spectral information is contained in a time-dependent signal that describes the decrease in the transverse magnetization. This signal can be converted into the conventional spectrum by Fourier transformation[93]. The technique requires only very short "exposures" of the order of 10—100 μs, and so allows the study of population changes produced by double resonance (Overhauser effects) and their relaxation processes. Since the H_1 pulse need only be applied after the perturbing field H_2 has been switched off, the Overhauser effects can be observed in this way without additional decoupling or tickling effects[94]. The importance of the use of the Fourier transform technique in double resonance experiments will undoubtedly increase in the future. It can be expected that Fourier-transformed ^{13}C-{^1H} pulse spectra in particular

will find a wide field of applications[95]. Besides the ^{13}C chemical shifts, spin-lattice relaxation times (T_1) of the individual carbon atoms also may be determined with this technique[96]. In this way a new parameter for structural studies becomes accessible.

4. Closing Remarks

Nuclear magnetic double resonance has developed during the past few years into a versatile research field. Whereas some of the techniques described here are already in routine use in commercial instruments, others require special instrumental arrangements. With the development of more versatile NMR spectrometers that are not designed only for the measurement of protons, more use will be made of heteronuclear double resonance experiments. This may be expected to lead in particular to rapid advances in carbon resonance, which holds a new dimension for organic chemistry. The broad spectrum of applications of double resonance to structural and spectroscopic problems has been illustrated in this article by a number of examples to provide the reader with a picture of the present situation. New methods and new applications may be foreseen for the future.

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COMMUNICATIONS

Crystal and Molecular Structure of Diethyl 2,4-Bis(diethylamino)cyclobutadiene-1,3-dicarboxylate[**]

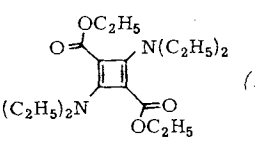
By *Hans Jörg Lindner* and *Brigitte von Gross*[*]

We have carried out an X-ray structure analysis to clarify the molecular structure of diethyl 2,4-bis(diethylamino)-cyclobutadiene-1,3-dicarboxylate *(1)*[1], which should provide further insight into the π-electron system of this compound. For these measurements single crystals were sealed under nitrogen in capillaries[2].

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Crystal data: yellow needles, m.p. 50–52 °C. $M = 338.2$, monoclinic; lattice constants: $a = 17.62$, $b = 13.81$, $c = 9.76$ Å, $\beta = 125.3°$, $U = 1954.2$ Å^3, $Z = 4$, $D_{calc.} = 1.1495$ g/cm^3.



(1)

Space group $P2_1/n$. The intensities of 2715 symmetry-independent reflections from layers 0...14 *kl* were measured with an automatic Weissenberg diffractometer with nickel-filtered Cu-K_α radiation; of these, 986 reflections were so weak that they could not be used for determination of structure.

The phases of 240 reflections with $E > 1.6$ were determined by *Karle* and *Karle*'s symbol addition method[3]. Fourier synthesis calculated with these E values and phases led to a complete structural model which has so far been refined to an R factor of 0.12 by Fourier syntheses and LSQ calculations[4].

The unit cell contains two pairs of symmetry-independent centrosymmetric molecules at two-fold special positions. The mean values of the bond lengths and bond angles of the two molecules are given in Fig. 1. Standard deviations for the bond lengths are 0.015 Å and for the bond angles 1°.

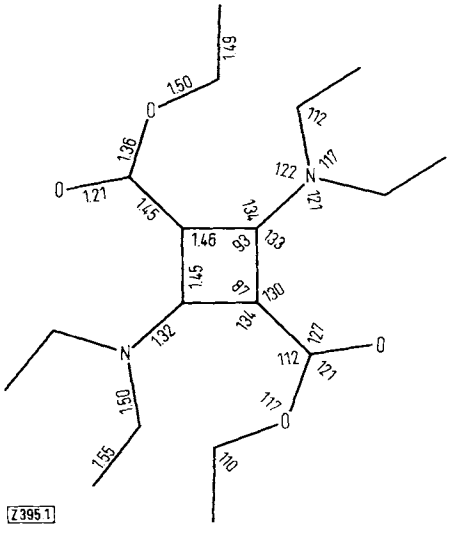


Fig. 1. Bond lengths and bond angles of *(1)*.

The four-membered ring of *(1)* contains, within experimental error, sides of equal length (1.46 Å) and angles of 93° and 87°. The C—N bond lengths indicate a high double-bond character. The C—C bonds between the four-membered ring and the ester groups are shortened.

The four-membered ring is planar within experimental error. Unlike the amino groups, the ester groups are displaced by about 20° from the plane of the four-membered ring.

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Dimethyl *N,N*-Dichlorophosphoramidate – A Warning

By *Hans Dieter Block* and *Reinhard Schliebs*[*]

Zwierzak et al.[1] synthesized dialkyl esters of *N,N*-dichlorophosphoramidic acid *(1)* by treating the corresponding dialkyl esters of phosphoramidic acid *(2)* with chlorine in aqueous, acetate-buffered solution.

We found that the diethyl ester of *(1)* is obtained in the form of a stable compound after distilling the reaction

$$(RO)_2P(O)NH_2 + 2\ Cl_2 \longrightarrow (RO)_2P(O)NCl_2 + 2\ HCl$$
(2) *(1)*

$R = CH_3;\ C_2H_5$

mixture and that its preparation does not present any problems, even on a kg scale.

Preparation of compound *(1)*, $R = CH_3$, on a 0.5-mole scale also proceeded in accordance with expectations. When working with 1.5 mole of starting material, on the other hand, a violent detonation took place after the reaction had gone to completion and after the mixture had been stirred for one hour.

The essential difference between the two preparations lay in the longer reaction time required when 1.5 mole of the starting material was reacted (6 hours as compared with 2 hours). It may be assumed that under these conditions either the amide *(2)*, $R = CH_3$, or the *N,N*-dichloroamide *(1)*, $R = CH_3$, undergoes partial hydrolytic cleavage of the P—N-bond, possibly leading to the formation of explosive nitrogen-chlorine compounds.

Zwierzak[2] himself never observed any explosive decomposition of *(1)*, $R = CH_3$; but on the other hand he never carried out any preparations using more than 0.15 mole.

It therefore seems advisable not to use amounts greater than about 0.2 mole when synthesizing *(1)*, $R = CH_3$, to keep the reaction time short and to observe the usual precautions for working with explosive substances.

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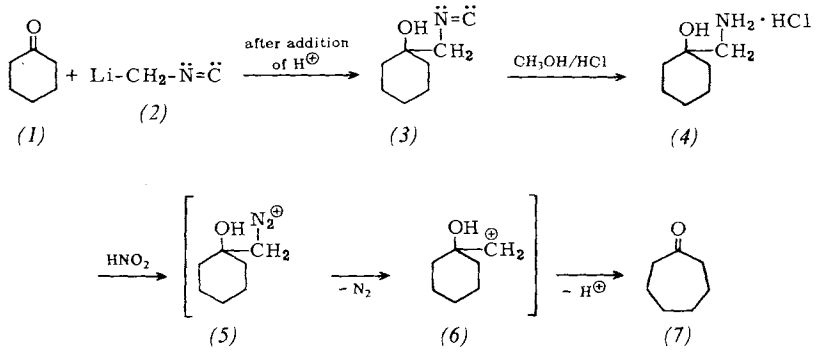
Homologation of Cyclic Ketones by Isocyanomethyllithium[1]

By *Ulrich Schöllkopf* and *Peter Böhme*[*]

Isocyanomethyllithium *(2)*, which is obtained from methyl isocyanide and butyllithium in tetrahydrofuran[2], provides a method of introducing aminomethyl groups into carbonyl compounds conveniently and in good yields[3,4]. From cycloalkanones one thus obtains 1-(aminomethyl)-1-cycloalkanols which, *inter alia*, are important as starting materials for *Tiffeneau-Demjanov* ring expansion[5]. For example, cyclohexanone *(1)* and *(2)* afford 1-(isocyanomethyl)-1-cyclohexanol (77% yield), which is converted by methanolic hydrogen chloride into the amine hydrochloride *(4)* (>63%). Diazotization with sodium nitrite in aqueous acetic acid then yields the intermediates *(5)* and *(6)* and finally cycloheptanone *(7)*. 1-(Isocyanomethyl) derivatives are obtained from cycloheptanone and cyclododecanone in 95% and 90% yield, respectively, and thence the amine hydrochlorides in about 80% and 67% yields respectively.

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This homologation could be more profitable than the route *via* the cyanohydrin[5,6] or the nitromethyl adduct[5,7], because the reaction of the ketone with *(2)* is irreversible



(1) *(2)* *(3)* *(4)* *(5)* *(6)* *(7)*

and the catalytic hydrogenation is replaced by a simple methanolytic process[8].

Cycloheptanone (7) from cyclohexanone (1):

Butyllithium (0.1 mol; 40.9 ml of a 2.45 N solution in pentane, cooled to −70 °C) is added dropwise to a stirred solution of methyl isocyanide (4.1 g, 0.1 mol) in anhydrous tetrahydrofuran (150 ml) kept under nitrogen at −60 °C. Cyclohexanone *(1)* (0.1 mol, 9.8 g) is added dropwise to this solution at such a rate that the temperature does not rise above −55 °C. After *ca.* 10 min glacial acetic acid (0.1 mol, 6 g) in tetrahydrofuran (10 ml) is dropped in, and the mixture is poured into ice-water (300 ml) and extracted with ether (3 × 100 ml). The ethereal extracts are dried over $MgSO_4$ and freed from solvent at water-pump vacuum (rotary evaporator). There remains the compound *(3)* (10.7 g, 77%) as a yellow oil, b.p. 80 °C/0.1 torr. IR spectrum (film): 2145 cm^{-1} (νNC); 3440 cm^{-1} (νOH).

Crude *(3)* (2 g, 14.4 mmol) is added portionwise (violent reaction!) to a solution of gaseous hydrogen chloride (2 g) in methanol (10 ml), then after 24 h at room temperature precipitation is effected by addition of ether (first *ca.* 50 ml, to provide crystals, and then a further *ca.* 100 ml). This provides in all 63% (1.5 g) of *(4)* as white platelets, m.p. 211 °C. On concentration of the mother liquor a further amount of *(4)* is obtained but this contains traces of *(1)* and is discarded.

The salt *(4)* (1.65 g, 10 mmol) is dissolved in water (15 ml) and glacial acetic acid (3 ml) and treated, under cooling by ice-salt, with a solution of $NaNO_2$ (1.04 g, 15 mmol) in water (5 ml)[7]. The mixture is left for 24 h and then allowed to come to room temperature, neutralized with $NaHCO_3$, and extracted with ether (3 × 70 ml). The extracts are dried over $MgSO_4$ and freed from solvent, affording the product *(7)* (0.8 g, 71.5%). IR spectrum (film): 1699 cm^{-1} (νCO), identical with that of an authentic specimen.

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[4] *P. Böhme*, Diploma Thesis, Universität Göttingen. For a synthesis of 1-amino-2-alkanols by way of oxazolines see *U. Schöllkopf*, Angew. Chem. *82*, 795, 804 (1970); Angew. Chem. internat. Edit. *9*, 763, 772 (1970).

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Synthesis of the Sex Attractant of *Ectocarpus siliculosus*[**]

By *Lothar Jaenicke, Timothy Akintobi*, and *Dieter G. Müller*[*]

The sperm attractant (sirenin) of the female gametes of the brown alga *Ectocarpus siliculosus* is a hydrocarbon $C_{11}H_{16}$ having the structure of an all-*cis*-1-(cyclohepta-2',5'-dienyl)but-1-ene *(1)*[1].

It has a center of asymmetry at the branching carbon atom. On account of the very small amounts of substance formed and given off by the sexually receptive female algae for a short time during the state of maturity, the optical rotation could not be determined. Considering its volatility, we ascribe to the compound the spherical (*S*)-structure *(1)*[2].

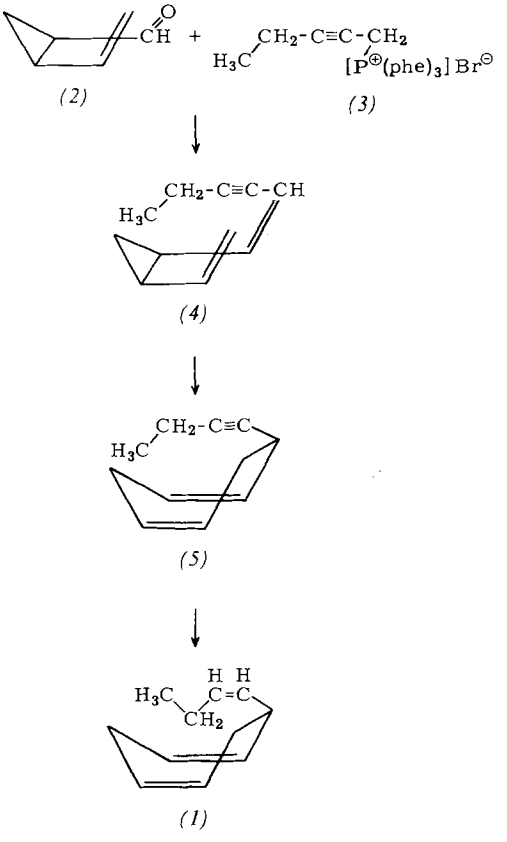
The compound is closely related to the dictyopterenes recently isolated by *Moore*[3] from the marine alga *Dictyopteris*. These substances are cyclopropane derivatives, $C_{11}H_{16}$, that can be converted into the corresponding cycloheptadienes by the Cope rearrangement, given the appropriate conformation of the *cis-trans*-isomers. In contrast, *Ectocarpus* gives off sirenin directly as the cycloheptadiene: Fractions of sirenin processed very carefully below room temperature do not display UV absorption above 200 nm and show the same NMR spectrum as the gas-chromatographically purified substance[2]. In particular, there is no indication of a cyclopropane structure between τ = 8.8 and 9.7 in the NMR spectrum.

In the meantime we have synthesized the racemate of the all-*cis*-1-(cyclohepta-2,5-dienyl)but-1-ene using the following method; Ethyl *cis,trans*-2-vinylcyclopropanecarboxylate is prepared from diazoacetic ester and butadiene by the method of *Vogel*[4]. Reduction to the carbinol by lithium alanate followed by oxidation with MnO_2 gives the *cis,trans*-2-vinylcyclopropanecarbaldehyde *(2)* which

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undergoes a Wittig reaction[5] with the triphenylphosphonium salt *(3)* from 1-bromo-2-pentyne[6] in benzene. The product *(4)* is isolated in 51% yield by vacuum distillation (80—91 °C/9 torr). Gas-chromatographic analysis (10% OV-225-cyano-silicone rubber on Chromosorb W)



(2) *(3)* *(4)* *(5)* *(1)*

shows it to contain the four anticipated isomeric cyclic hydrocarbons $C_{11}H_{14}$. The mixture of isomers is hydrogenated in methanol over a Lindlar catalyst. By preparative gas chromatography (10% Apiezon L on Chromosorb B), the fraction having the same retention time as the *Ectocarpus* sirenin is separated from the mixture of isomers (yield: 30% calculated on the amount of starting material). Its physical properties and odor are identical with those of the natural hydrocarbon *(1)* obtained from *Ectocarpus siliculosus*.

The retention indices of the synthetic cycloheptadienylbutene *(1)* correspond to those of natural sirenin on polar and apolar columns. NMR spectrum: A triplet corresponding to three protons appears at $\tau = 9.05$ ($-CH_3$); a multiplet corresponding to two protons at 8.0 (CH_3-CH_2-); a multiplet at 4.7 corresponding to two protons ($CH_3-CH_2-CH=CH-$); a complex multiplet at 6.55 (one proton) ($-CH=CH-CH(CH-)_2$); a multiplet at 4.45 corresponding to four protons

($-CH=CH-CH_2-CH=CH-$);

a complex multiplet at 7.2 (two protons)

($-(CH=CH)_2CH_2-$);

a multiplet at 7.8 corresponding to two protons

($-CH=CH-CH_2-CH<$).

For the NMR spectrum of the natural product cf.[1].

The structure *(1)* given for the *Ectocarpus* sirenin[1] is thus confirmed by the synthesis[***].

[***] We wish to thank Prof. *E. Vogel* for his interest and advice, and Dr. *M. Donike* for ready help.

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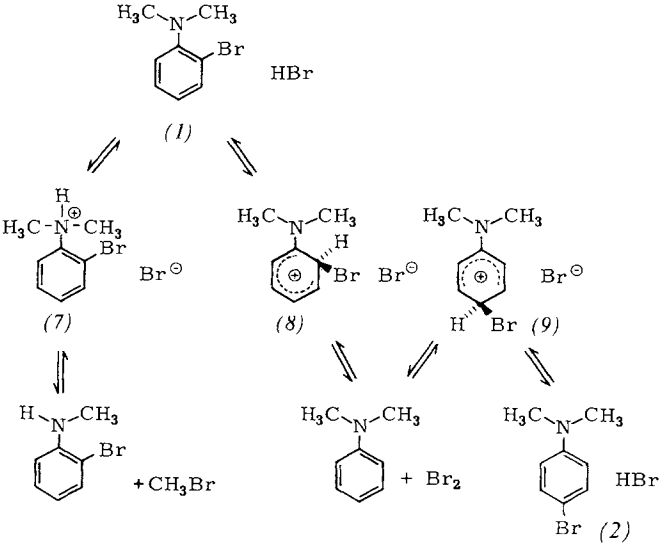
Reversibility of the Bromination of *N*-Alkylanilines[1]

By *Franz Effenberger* and *Peter Menzel*[*]

Except for alkylation, sulfonation, and iodination, electrophilic substitution of aromatic compounds is held to be irreversible[2]. However, isomerization, disproportionation, and dehalogenation have also been observed when brominated aromatic compounds are heated in the presence of Lewis acids[3].

Stabilization of the intermediate σ-complexes which may be influenced by steric and electronic factors is essential for ease of the reverse reaction in electrophilic substitutions[3,4]. Since NR_2 substituents stabilize cationic intermediates particularly effectively[5], isomerization and dehalogenation are most likely to be observed with *N,N*-dialkylhaloanilines.

Upon heating 0.1 M solutions of the hydrobromides *(1)* to *(6)* in $CHCl_3$ at 120 °C in a sealed vessel for 3 hours, the aniline mixtures listed in Table 1 are obtained; even under these rather mild conditions we find large amounts of



(1) *(7)* *(8)* *(9)* *(2)*

isomerization, dehalogenation, and dealkylation products. Though much slower, these reactions take place already at 80 °C; at 60 °C, 160 hours' heating is necessary to effect significant changes.

Isomerization and disproportionation of *p*-bromophenols at room temperature have recently been reported[6]. In

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view of our results, however, this does not seem to be a true reversal of aromatic substitution by way of σ-complexes; an alternative route *via* tautomeric quinonoid intermediates is rather more likely. The efficiency of substituents in stabilizing a positive charge in the transition state is given by the σ_p^+ values which are −0.92 for OH and −1.70 for $N(CH_3)_2$[7]. Thus, reversibility of electrophilic bromination of phenols should be achieved only under appreciably more vigorous conditions than those required for *N,N*-dialkylanilines.

Our results show the electronic influence of the NR_2 group to be decisive for isomerization and dealkylation. Due to steric hindrance of mesomerism, *ortho*-substituents favor *N*-protonation and thus dealkylation, as shown by the reactions of *(4)* and *(6)*.

Table 1. Mixtures of anilines obtained by heating the anilinium bromides *(1)* to *(6)*.

Hydrobromide of	Products (mol-%) [a] -*N,N*-dimethylaniline		-*N*-methylaniline		-aniline	
2-Bromo-*N,N*-dimethylaniline *(1)*	2-Br	8.2 (4.2) [b]	2-Br	22.9 (16.5) [b]		
	4-Br	35.0 (14)	4-Br	5.8 (8.5)		
	2-H	16.3 (18)	2-H	3.7 (13.0)		
			2,4-Br_2	8.1 (19.5)		
4-Bromo-*N,N*-dimethylaniline *(2)*	4-Br	75.0	4-Br	4.8		
	4-H	13.4				
	2,4-Br_2	2.3	2,4-Br_2	4.5		
2,4-Dibromo-*N,N*-dimethylaniline *(3)*	2,4-Br_2	35.4	2,4-Br_2	50.3		
	4-Br	14.3				
2,6-Dibromo-*N,N*-dimethylaniline *(4)*	2,6-Br_2	30.0	2,6-Br_2	54.3	2,6-Br_2	10.1
			2-Br	5.6		
2,4-Dibromo-*N*-ethyl-*N*-methylaniline *(5)*			2,4-Br_2	6.6	2,4-Br_2-*N*-Et-*N*-Me	33
					4-Br-*N*-Et-*N*-Me	20
					2,4-Br_2-*N*-Et	30
					aniline	8
2,6,*N,N*-Tetramethylaniline *(6)*	2,6-Me_2	75.6	2,6-Me_2	24.4		

[a] The bases were liberated by passing in NH_3; the product composition was determined by gas chromatography, the individual compounds being identified by comparison of the retention times with those of pure substances. *W. Blum* has confirmed the assignments by a GC-MS combination Finnigan system DA-150.

[b] Product compositions in parentheses are those obtained after heating for 160 hours at 120 °C.

We assume the anilines obtained to be formed *via* cationic intermediates *(7)–(9)*, as formulated for reaction of *(1)* in the above scheme. In an S_N2 reaction cation *(7)* is dealkylated by the $Br^{\ominus}$. *C*-Protonation of *(1)* affording *(8)* is followed by dehalogenation to dimethylaniline which then gives the isomerization product *(2) via (9)*. Incorporation of labeled $^*Br$ in the course of the reaction of *N,N*-dimethyl-*p*-bromoaniline·H*Br is proof that *(2)* may be dehalogenated again by way of *(9)*, and that free Br_2 must occur during the overall reaction. The large proportion of starting material recovered when *(2)* is heated must be ascribed to preferential rebromination of dimethylaniline at the *para*-position. Longer reaction times favor dealkylation, as shown by the product composition after 160 hours' heating of *(1)* at 120 °C. These also are not equilibrium concentrations, though, since irreversible oxidations (discoloration) become more and more pronounced with longer reaction times.

Since CH_3 rather than C_2H_5 is lost preferentially from *(5)*, the dealkylation is indicated to be of S_N2 type. If HBr is replaced by acids with less nucleophilic anions, the share of isomerization and dealkylation products decreases; *N,N*-dialkylbromoanilinium perchlorates remain practically unchanged under our experimental conditions.

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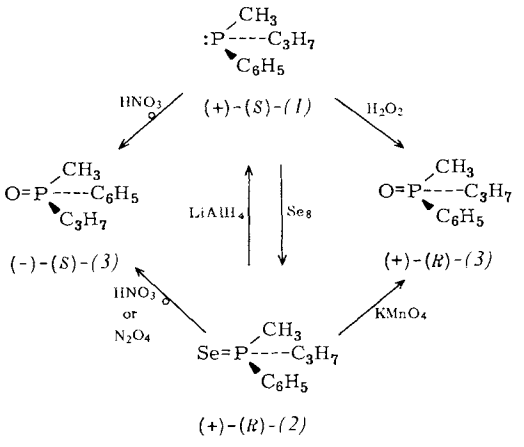
Optically Active Selenoxomethylphenylpropylphosphoranes and Their Transformations

By *W. Stec, A. Okruszek*, and *Jan Michalski*[*]

We have found that the previously unreported[1] optically active selenoxotriarylalkyl(triaryl-)phosphanes can be readily obtained by addition of elemental selenium to optically active tertiary phosphanes. Since the stereochemistry of the addition of selenium to phosphanes was obscure, some additional studies on the transformation of optically active selenoxotriarylalkyl(triaryl-)phosphanes were considered necessary. Correlation of known absolute configurations of phosphanes[2] and oxophosphoranes[2] with those of selenoxophosphoranes was therefore undertaken. Optically active selenoxophosphoranes can be readily converted into the corresponding oxophosphoranes by two stereoselective routes, as well as reduced stereoselectively to the parent phosphanes (Scheme 1).

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Treatment of (+)-(*S*)-methylphenylpropylphosphane *(1)*[3], $[\alpha]_{578}^{20} = +17.3°$ (toluene) with stoichiometric amounts of elemental selenium in benzene gave (+)-(*R*)-selenoxomethylphenylpropylphosphane *(2)*[4], $[\alpha]_{578}^{20} = +16.9°$[5], m. p.



Scheme 1

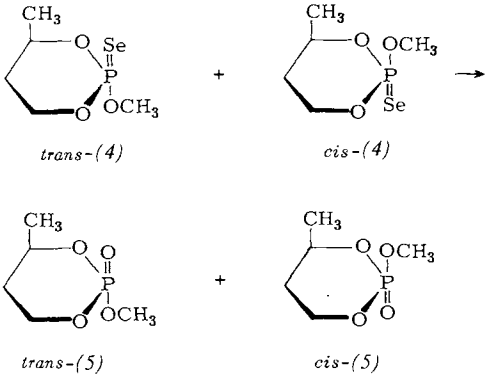
60–75 °C, while addition of selenium to (−)-(*R*)-*(1)*, $[\alpha]_{578}^{20} = -9.0°$ (toluene), produced (−)-(*S*)-*(2)*, $[\alpha]_{578}^{20} = -8.8°$, m. p. 55–75 °C. Multiple fractional crystallization of compounds *(2)* from cyclohexane improved their optical purity. Both enantiomers of *(2)* have m. p. 75–76 °C and $[\alpha]_{578}^{20}$ (+ or −) 20.2°.

The compound (+)-(*R*)-*(2)*, $[\alpha]_{578}^{20} = +19.7°$, is readily reduced by $LiAlH_4$ in boiling THF to (+)-(*S*)-*(1)*, $[\alpha]_{578}^{20} = +17.8°$ (toluene). The same reduction of (−)-(*S*)-*(2)*, $[\alpha]_{578}^{20} = -20.2°$, gave (−)-(*R*)-*(1)*, $[\alpha]_{578}^{20} = -18.65°$ (toluene). The yields of both reactions were over 80%. An attempt to reduce the selenoxophosphoranes *(2)* with other reducing agents such as Raney-Ni or $SiHCl_3/(C_2H_5)_3N$ were partially successful only in the former case[6].

Oxidation of the optically active selenoxophosphoranes *(2)* with nitric acid[8] and with potassium permanganate in aqueous pyridine[7] proceeds *via* stereochemically different courses. When (−)-(*S*)-*(2)*, $[\alpha]_{578}^{20} = -11.3°$, was treated with $KMnO_4$ in pyridine/water (2:1) v/v), (−)-(*S*)-oxomethylphenylpropylphosphorane *(3)*, $[\alpha]_{578}^{20} = -9.7°$, was formed. The same enantiomer *(2)*, $[\alpha]_{578}^{20} = -20.2°$, oxidized with HNO_3 gave (+)-(*R*)-*(3)*, $[\alpha]_{578}^{20} = +17.9°$. Treatment of (+)-(*R*)-*(2)*, $[\alpha]_{578}^{20} = +20.2°$, with HNO_3 produced (−)-(*S*)-*(3)*, $[\alpha]_{578}^{20} = -17.9°$. Oxidation with N_2O_4 followed a similar stereochemical course to that with HNO_3. Thus, from (+)-(*R*)-*(2)*, $[\alpha]_{578}^{20} = +20.2°$ the oxophosphorane (−)-(*S*)-*(3)*, $[\alpha]_{578}^{20} = -3.2°$ was isolated after treatment with a 10% solution of N_2O_4 in CH_2Cl_2. (−)-(*S*)-*(2)*, $[\alpha]_{578}^{20} = -20.2°$, gave (+)-(*R*)-*(2)*, $[\alpha]_{578}^{20} = +5.6°$. The considerable racemization is undoubtedly caused by action of N_2O_4 on the resulting oxide *(3)*[8].

Since the stereochemistry of the oxidation of phosphane *(1)* with HNO_3[8] and with H_2O_2[2] is well established we conclude from our experiments that addition of selenium to optically active tertiary phosphanes proceeds with retention of configuration. The absolute configuration *R* has been therefore assigned for dextrorotatory selenoxophosphorane *(2)*. A retention mechanism is also proposed for reduction of the selenoxophosphorane *(2)* to parent phosphane as well as for its oxidation with $KMnO_4$ in pyridine/water solution to the corresponding oxophosphorane, while oxidation of *(2)* with HNO_3 or N_2O_4 proceeds *via* inversion.

Close analogy of the stereochemical transformations is observed in the case of the corresponding thioxophosphoranes, except for the oxidation with N_2O_4. Since only little is known about the mechanism of oxidation of phosphanes and the thioxo- and selenoxophosphoranes with the oxidizing agents mentioned above, interpretation of this observation is difficult.



Scheme 2.

In contrast to the oxidation of acyclic selenoxophosphoranes *(2)* described above oxidation of diastereomeric 2-methoxy-4-methyl-4*H*-5,6-dihydro-1,3,2-dioxaphosphorin 2-selenides *(4)* to the oxides *(5)*[9] is highly stereoselective; an epimerization was not observed[10].

trans-(4) (%)	*cis-(4)* (%)	Reagent	*trans-(5)* (%)	*cis-(5)* (%)
83.5	16.5	N_2O_4	79.0	21.0
83.5	16.5	HNO_3	81.0	19.0
22.0	78.0	N_2O_4	25.0	75.0
22.0	78.0	HNO_3	25.0	75.0

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[2] *L. Horner*, Pure Appl. Chem. *9*, 225 (1964).

[3] Optically active phosphanes *(1)* were prepared by alkaline hydrolysis of diastereoisomeric benzylmethylphenylpropylphosphonium dibenzoyltartrates (*K. F. Kumli, W. E. McEwen*, and *C. A. Vander Werf*, J. Amer. Chem. Soc. *81*, 248, 3805 (1959)) followed by reduction of the oxophosphoranes *(3)* with $SiHCl_3/(C_2H_5)_3N$ (*L. Horner* and *W. D. Balzer*, Tetrahedron Lett. *1965*, 1157).

[4] Both selenoxophosphoranes *(2)* gave the correct elemental analysis and NMR spectra and their purity was checked by thin-layer chromatography.

[5] Rotations refer to solvent methanol unless otherwise stated.

[6] The reduction of racemic *(2)* with 5-fold excess of Ni-Raney in boiling ethanol for 7 hours yielded only 27% of *(1)*.

[7] Retention of configuration during oxidation of methylphenylpropylthioxophosphorane with $KMnO_4$ in pyridine has been described by *L. Horner* [2].

[8] The procedure for oxidation with HNO_3 and N_2O_4 was identical to that described for transformation of the corresponding optically active thioxophosphoranes (*J. Michalski, A. Okruszek*, and *W. Stec*, Chem. Comm. *1970*, 1495).

[9] *W. Stec, A. Okruszek*, and *M. Mikołajczyk*, Z. Naturforsch., in press.

[10] *(4)* was prepared by addition of elemental selenium to 2-methoxy-4-methyl-4*H*-5,6-dihydro-1,3,2-dioxaphosphorin; *cis-(4)*: b. p. 85—87 °C/0.2 torr, NMR ($CDCl_3$): $\delta(OCH_3) = 3.8$ ppm, $J_{POCH} = 14.4$ Hz; *trans-(4)*: b. p. 100—102 °C/0.2 torr, NMR ($CDCl_3$): $\delta(OCH_3) = 3.7$ ppm, $J_{POCH} = 14.4$ Hz. The ratio of the diastereomeric dioxaphosphorins *(4)* and *(5)* (±5%) was determined by gas-liquid chromatography.

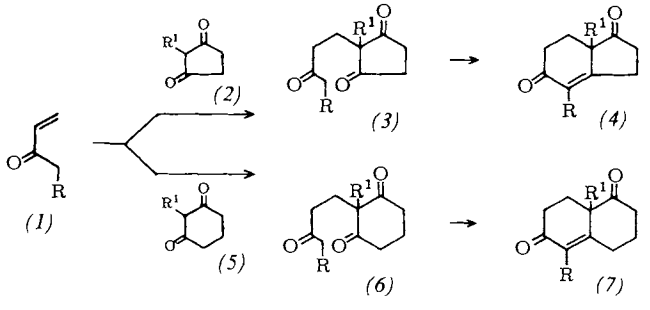
New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures[**]

By *Ulrich Eder*, *Gerhard Sauer*, and *Rudolf Wiechert*[*]

Synthesis of optically active 7a-alkyl-5,6,7,7a-tetrahydro-1,5-indandiones *(4)* and 8a-alkyl-1,2,3,4,6,7,8,8a-octahydro-1,6-naphthalenediones *(7)*, which are important CD starting materials for total synthesis of steroids[1-5], has hitherto been effected from the racemic bicyclics *(4)* and *(7)*, respectively, by microbiological transformation of one antipode[7] or by conventional resolution of the racemate[2,4]. Both methods give at best 50% yields based on the amounts of starting material.

Compounds *(3)* and *(6)* each contain a prochiral center which should be utilizable in an economical process for preparation of the chiral bicyclics *(4)* and *(7)*.

In the synthesis of compounds *(3)* and *(6)* by Michael addition of the vinyl ketones *(1)* to the cyclic 1,3-diketones *(2)* and *(5)* the yield and purity of the products could be



appreciably increased by working in an aqueous medium without a basic catalyst.

Table 1. Compounds synthesized.

Substrate	Amine component	Reaction conditions	Yield (%) chem.		opt.	$[\alpha]_D^{RT}$ (°)
(3a)	L-α-Methylbenzylamine	CH_3COOH, 2 h, 100 °C	81	*(4a)*	45	+163 [2, 7]
(3a)	L-Proline	CH_3CN, 1 N $HClO_4$, 22 h, 80 °C	86.6	*(4a)*	84	+304 [2, 7]
(3a)	D-Proline	CH_3CN, 1 N $HClO_4$, 20 h, 80 °C	75	*(4a)*	67	−242 [2]
(3b)	L-Proline	DMF, 1 N HCl, 7 h, 100 °C	76	*(4b)*		+210
(3c)	L-Alanine	CH_3CN, 1 N $HClO_4$ 70 h, 80 °C	69	*(4c)*		+202
(3d)	L-Phenylalanine	CH_3CN, 1 N $HClO_4$ 43 h, 80 °C	60	*(4d)*		+181
(3e)	L-Phenylalanine	CH_3COOH, 4 h, 120 °C	55	*(4e)*	64	+154 [8]
(6a)	L-Proline	CH_3CN, 1 N $HClO_4$ 25 h, 80 °C	83	*(7a)*	71	+ 72 [7]
(6b)	L-Proline	CH_3COOH, 3 h, 100 °C	61	*(7b)*		+ 12

in our chiral accessories induced the (*R*)-configuration. The "chiral induction" was found to be strongly dependent on the substrate, amine component, solvent, and acid. The molecular proportion of substrate to amino compound is,

	(a)	*(b)*	*(c)*	*(d)*	*(e)*
(1)	R = H	R = CH_3	R = CH_2—CH_2—C_6H_4—OCH_3-*m*	R = CH_2—CH_2—$COOCH_3$	
(2)	R^1 = CH_3	R^1 = C_2H_5			
(3)	R = H, R^1 = CH_3	R = H, R^1 = C_2H_5	R = CH_3, R^1 = CH_3	R = CH_2—CH_2—C_6H_4—OCH_3-*m*, R^1 = CH_3	R = CH_2—CH_2—$COOCH_3$, R^1 = CH_3
(4)	R = H, R^1 = CH_3	R = H, R^1 = C_2H_5	R = CH_3, R^1 = CH_3	R = CH_2—CH_2—C_6H_4—OCH_3-*m*, R^1 = CH_3	R = CH_2—CH_2—$COOCH_3$, R^1 = CH_3
(5)	R^1 = CH_3	R^1 = *n*-C_4H_9			
(6)	R = H, R^1 = CH_3	R = H, R^1 = *n*-C_4H_9			
(7)	R = H, R^1 = CH_3	R = H, R^1 = *n*-C_4H_9			

As chiral accessory that effects the asymmetric cyclization we first used optically active primary and secondary amines, which fulfil this role very well in the presence of organic or aqueous inorganic acids. However, use of natural amino acids (see Table 1) proved even more effective.

The (*S*)-amines and (*S*)-amino acids induce the (*S*)-configuration in the bicyclics *(4)* and *(7)*; the (*R*)-configuration

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[6] After conclusion of our work we learned that a research group at Hoffmann La Roche Inc. (Nutley, N. J., USA) has also developed a method for synthesis of the optically active bicyclics.

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[8] US-Pat. 3413314 (1968), Roussel-Uclaf.

however, variable over a wide range (1:0.1 to 1:2) and its effect is mainly on the reaction time[6].

Experimental:

A solution of 2-methyl-2-(3'-oxobutyl)-1,3-cyclopentanedione *(3a)* (10 g) in acetonitrile (150 ml) was treated with L-proline (3 g) and 1 N $HClO_4$ (15 ml) and refluxed for 22 h. The mixture was then cooled and diluted with saturated sodium chloride solution. The crude product was distilled off in a high vacuum. Yield 7.81 g of *(4a)*, b.p. 97—100 °C/0.01 torr. $[\alpha]_D^{RT} = +303°$ (1% in C_6H_6). Optically pure *(4a)*, m.p. 65—66.5 °C, $[\alpha]_D^{RT} = +362°$ (1% in C_6H_6)[2, 7] (5.9 g), was obtained by crystallization.

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Calculation of the Intermediates and Transition State in Electrophilic Aromatic Substitution[1]

By *Werner Jakubetz* and *Peter Schuster*[*]

Dedicated to Prof. M. Pailer on the occasion of his 60th birthday

The cation $[C_6H_7]^+$ has long been postulated as intermediate in electrophilic hydrogen exchange of benzene and constitutes the simplest transition state in the course of electrophilic aromatic substitutions[2]. It was recently detected in solution by use of $[SbF_6]^-$ as counter-ion[3].

(except the CH distances for the protons not concerned in the exchange) and the most important angles were optimized for the energy minimum and the transition state.

The energy minimum corresponds to a Dewar-type π-complex[6]. The seventh proton is out of the plane of the ring and exactly above the center of a C—C bond. The other bond lengths in the ring alternate; the whole cation is folded along an axis through C-3 and C-6, with a dihedral angle $\alpha = 178.6°$. The excess proton has the lowest electron density ($q_H = +0.27$). It is interesting that the bridge protons in B_2H_6 carry a similar charge ($q_H = +0.20$). The rest of the charge on the cation is distributed almost uniformly over all the other atoms. CNDO/2 minimum geometry and charge distributions are shown in Figure 1.

From our calculations it follows that the saddle point of the energy surface and thus the transition state of the substitution reaction is identical with the optimized σ-complex. The bond lengths accord with expectation. The positive charge is distributed over the seven H atoms and the C atoms 2, 4, and 6 in alternating manner typical of charged π-electron systems.

As the CNDO calculation shows, transition of the π-complex into the σ-complex requires an energy of ~20 kcal/mol. If a π-complex were converted into an equivalent one without proton exchange occurring, an energy of only ~15 kcal/mol would need to be provided. Such energy differences, however, carry systematic errors, but are nevertheless very useful as relative values[1, 5]. For π-complexes and related structures the numerical values are always too large, so we expect that the six equivalent

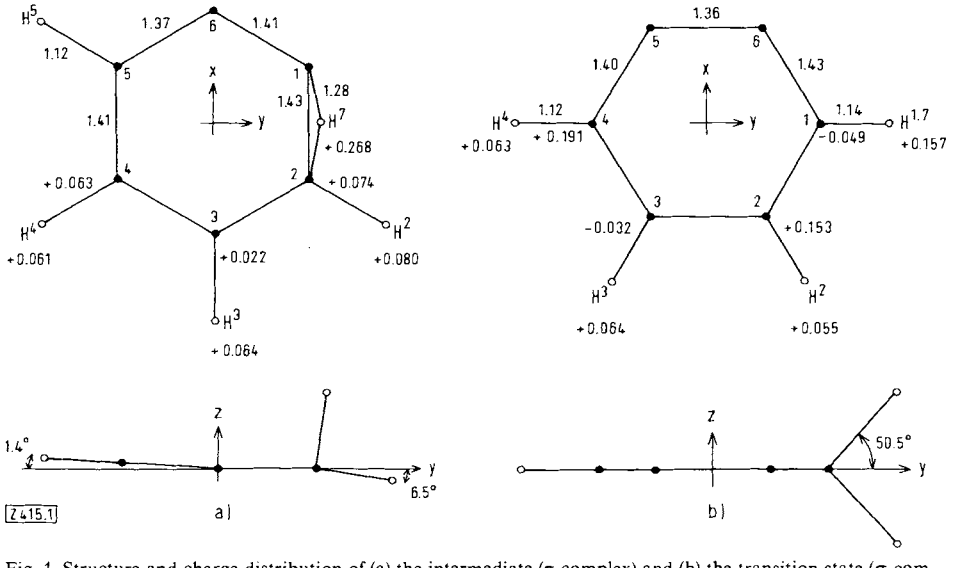


Fig. 1. Structure and charge distribution of (a) the intermediate (π-complex) and (b) the transition state (σ-complex) in the reaction $C_6H_6 + H^+$ (bond lengths in Å; all C—H separations in the ring plane are assumed as 1.12 Å, as in the CNDO energy minimum of benzene).

For comparison: C_6H_6: $R_{CC} = 1.38$; $R_{CH} = 1.12$ Å; $q_C = +0.011$, $q_H = -0.011$. — B_2H_6: $R_{BB} = 1.60$, R_{BH}(bridge) $= 1.33$, R_{BH}(ext.) $= 1.16$ Å; $q_B = -0.065$, q_H(bridge) $= +0.196$, q_H(ext.) $= -0.065$.

For study of this intermediate the energy surface for interaction of benzene and H^+ has been calculated point by point. We selected the semi-empirical method of *Pople et al.*[4]—CNDO/2—as we obtained good results with this method of calculation for description of hydrogen bridges[5] and weak π-complexes[1]. All the bond lengths

π-complexes would rapidly rearrange at room temperature.

To provide more information about the bonding of the seventh proton in the complex $[C_6H_7]^+$ the canonical SCF molecular orbitals were localized by *Boys'* method[7]. Together with the two nearest C atoms this proton forms a three-center bond which takes up two electrons and is surprisingly similar to the "hydride bridges" in diborane, B_2H_6 (Table). For the case of B_2H_6 it is possible to compare

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the CNDO/2 and *ab-initio* calculations[8], which show the reliability of the approximation chosen.

In the ^{1}H-NMR spectrum of the cation $[C_6H_7]^+$ *Olah et al.*[3] found at room temperature one single signal which was split at lower temperatures. These authors

Table. Localized three-center molecular orbitals.

Atom	Function	Linear combination coefficients $[C_6H_7]^+$	B_2H_6	B_2H_6, *ab initio* [8] [a]
C^1, B^1	2 *s*	0.2419	0.2701	0.1569
	2 p_x	0.2595	0.3069	0.1995
	2 p_y	0.0404	0	0
	2 p_z	0.4208	0.3632	0.2143
H	1 *s*	0.5980	0.6315	0.5600
C^2, B^2	2 *s*	0.2419	0.2701	0.1569
	2 p_x	−0.2595	−0.3069	−0.1995
	2 p_y	0.0404	0	0
	2 p_z	0.4208	0.3632	0.2143
Localized proportion (%)		96.7	99.7	

[a] The linear combination coefficients of CNDO calculations refer to orthogonalized (Löwdin) atomic orbitals and thus their absolute values in bonding molecular orbitals are greater than the corresponding coefficients in *ab-initio* calculations which refer to ordinary non-orthogonal atomic orbitals.

assigned the structure of a σ-complex to the solvated cation. According to our calculations the π-complex should be more stable in the gas phase. This need not contradict our results since π- and σ-complexes can differ considerably in their solvation energies and in their interaction with the counter-ion.

Recently *Helgstrand*[9] reported CNDO/2 calculations on the σ-complex of $[C_6H_7]^+$. This author's results agree well with ours, especially as regards bond angles and CH distances.

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[8] *E. Switkes, R.M. Stevens, W.N. Lipscomb*, and *M.D. Newton*, J. Chem. Phys. *51*, 2085 (1969).

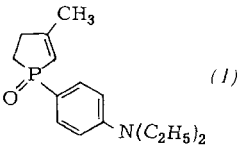
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An Optically Active Phospholene Oxide

By *G. Ostrogovich* and *F. Kerek*[*]

We have been able to prepare the levorotatory form of 3-methyl-1-(*p*-diethylaminophenyl)-2-phospholene 1-oxide *(1)* *via* its salt with (+)-9-camphorsulfonic acid. To the best of our knowledge this is the first resolution of a chiralic phosphacyclic compound[1].

Methylene chloride solutions of *(1)*[2, 3] (16.5 mmol in 10 ml) and (+)-9-camphorsulfonic acid (previously dried in vacuum over P_2O_5; 16.2 mmol in 160 ml) were thoroughly



(1)

mixed and the solvent subsequently removed in vacuum. The residual syrup was dissolved in 75 ml boiling benzene and the hot solution rendered slightly turbid by addition of 3–4 ml *n*-heptane. By very slow and careful cooling, approximately 4.1 g of the camphorsulfonate of *(1)* could be obtained.

After double recrystallization from benzene with a little *n*-heptane the specific rotation and melting point were constant ($[\alpha]_D^{20} = -40.3°$ (benzene); m.p. 103–104 °C). The difference between the UV spectrum (in cyclohexane) of compound *(1)* ($\lambda_{max} = 277$ nm; $\log \varepsilon = 4.45$) and that of the salt ($\lambda_{max} = 281$ nm; $\log \varepsilon = 3.03$) shows that an ammonium (and no phosphonium) salt is present.

The (−)-enantiomer of *(1)* recovered by treatment with dilute KOH was extracted with $CHCl_3$ and, after removal of solvent, recrystallized twice from *n*-heptane ($[\alpha]_D^{20} = 69.4°$ (0.6 mol/l in benzene). The ORD curve is given in Figure 1.

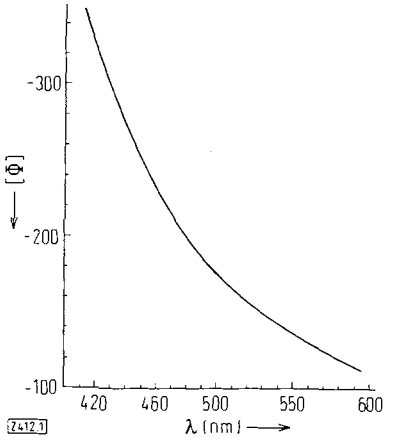


Fig. 1. ORD spectrum of (−)-3-methyl-1-(*p*-diethylaminophenyl)-2-phospholene 1-oxide, (−)-*(1)*, in anhydrous ethanol [7].

The similarity in constitution of (−)-*(1)* and racemic *(1)* was established from the IR, UV[5, 6], and NMR[4, 6] [$\tau = 5.88$ ppm (vinyl H), $J_{PH} = 25$ Hz] spectra and by elemental analysis[2].

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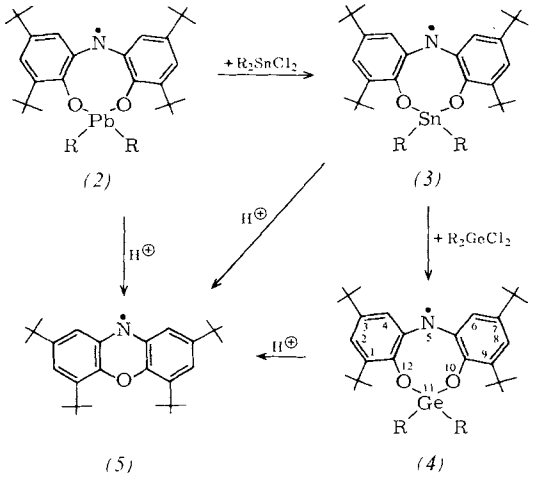
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Crystalline π-Radicals Containing Germanium[**]

By *Hartmut B. Stegmann, Klaus Scheffler,* and *Fritz Stöcker*[*]

No success has previously attended attempts to prepare paramagnetic organogermanium compounds by, in particular, dissociation of hexaaryldigermanes[1]. Hyperfine structure that could be ascribed to magnetic coupling of a free electron with ^{73}Ge has never been found in ESR studies of radical anions containing germanium[2] or of Ge-substituted alkyl radicals[3-5]. We have, however, now isolated paramagnetic compounds containing germanium as products of the reaction of 2-amino-4,6-di-*tert*-butylphenoxyl *(1)* with diarylgermanium dihalides. Structure *(4)* is indicated by elemental analysis[6], mass spectra, and chemical behavior.

The new compounds can also be prepared from the corresponding tin[7] and lead compounds[8] when these are treated with diarylgermanium halides.



(4a), R = C_6H_5, m. p. 196 °C; *(4b)*, R = p-$CH_3C_6H_4$, m. p. 241 °C

The radicals *(2)* to *(4)* are stable, so that they can be isolated without special procedures. The diamagnetic N—H heterocycles are formed on reduction by H_2/Pt and are at once oxidized by atmospheric oxygen back to the radicals. Concentrated mineral acids degrade the radicals. Elimination of the organometallic group affords the phenoxazinyl radical *(5)*[9] without loss of the paramagnetism being observed.

The radicals *(4a)* and *(4b)* in ethanol or benzene afford first a 15-line ESR signal. This hyperfine structure (HFS) (Fig. 1) can be interpreted as due to magnetic coupling of the free electron with two pairs of protons and the ^{14}N nucleus.

HFS components that could be ascribed to Ge coupling are to be expected only at increased sensitivity. In the natural isotope mixture there is only one magnetic nucleus, ^{73}Ge, in 7.6% amount. This isotope has nuclear spin $I = 9/2$, so that the ten Ge-HFS components can be observed with very weak intensity only at the edges of the spectra and, further, are split by the protons and nitrogen present in the molecule. Actually, with 390-fold increase in spectrometer sensitivity, further HFS components that we

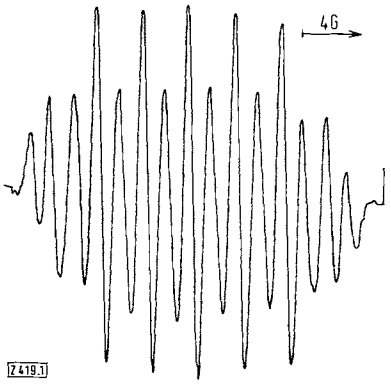


Fig. 1. ESR spectrum of *(4a)* in benzene at room temperature.

ascribe to the ^{73}Ge can be found both on the low-field and on the high-field side of the main spectrum (Fig. 2).

Since the magnetic coupling with the ^{73}Ge is relatively small, each of the two lines furthest from the center are single and correspond to the terms $m_{^{73}Ge} = +9/2$ and

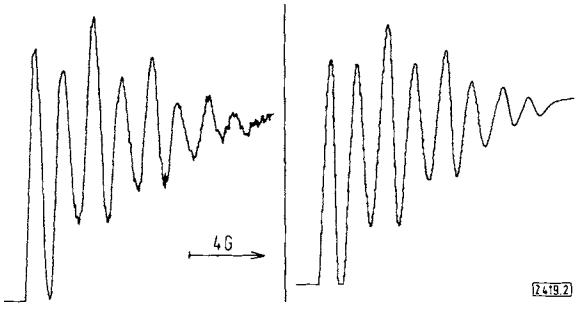


Fig. 2. Left: high-field side of the ^{73}Ge isotope spectrum of *(4a)* in benzene at room temperature. Right: simulated high-field isotope spectrum.

$-9/2$. The remainder of the isotope spectrum is degraded. The HFS found is in very good agreement with these considerations, as the simulation[10] (Fig. 2) of the spectrum shows.

In accord with the other findings, the ESR spectrum shows the new organogermanium derivatives to be 11,11-disubstituted 1,3,7,9-tetra-*tert*-butyldibenzo[*d*,*g*][1,3,6,2]dioxagermanocin-5-yls. The coupling parameters are

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

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[3] *A. Hudson* and *H. A. Hussain*, J. Chem. Soc. *B 1969*, 793.
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[9] *H. B. Stegmann, K. Scheffler, F. Stöcker*, and *H. Bürk*, Chem. Ber. *101*, 262 (1968); *K. Scheffler* and *H. B. Stegmann*, Tetrahedron Lett. *1968*, 3619.
[10] The spectrum simulation was carried out on the CDC 3300 at the Zentrum für Datenverarbeitung, Universität Tübingen (Germany).

ascribed by us principally by analogy with the corresponding tin compounds[7] (Table 1).

As expected, the substituent R has only slight influence on the coupling constants. The large line widths (*ca.* 700 mG) may be ascribed to the unresolved proton HFS of the

Table 1. ESR data for the radicals *(4)* (gauss), measured in benzene at room temperature; ΔH = line width.

	$a_{H_{4,6}}$	$a_{H_{2,8}}$	a_N	$a_{^{13}C}$	g	ΔH
(4a)	1.36	3.02	6.13	3.02	2.002906	0.65
(4b)	1.41	3.01	6.27	3.44	2.002978	0.72

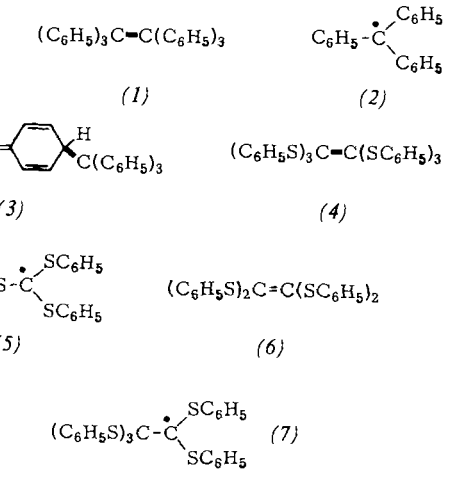
tert-butyl groups; intramolecular movements are not the cause of the line widening because the spectra are almost unchanged between -70 and $+120$ °C.

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Homolysis of the Ethane C—C Bond: Detection of Tris(phenylthio)methyl by ^{13}C-Labeling[**]

By *Dieter Seebach, Hartmut B. Stegmann,* and *Albert K. Beck*[*]

Since the beginning of the century hexaphenylethane *(1)* has been held to be the simplest ethane whose C—C bond dissociates already at room temperature. However, it was shown recently[1] that the trityl radical *(2)*[2] really dimerizes to *(3)*[3]. We have reported[4] that the persubstituted ethane *(4)* at slightly above 100 °C affords a radical that is readily detected by ESR spectroscopy; we have assigned the spectrum, which shows no hyperfine structure, to the methyl *(5)* mainly on the basis of chemical findings: four



(1) *(2)* *(3)* *(4)* *(5)* *(6)* *(7)*

of the five products isolated in >95% yield after pyrolysis of *(4)* are derived from the "half molecule"[5]; the fifth is the ethylene *(6)* which could arise directly from the ethane *via (7)*.

By using the ethane labeled by ^{13}C on the central atoms we can now answer the following questions:

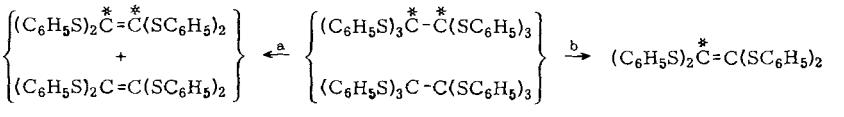
1) Do we really observe the ESR spectrum of the methyl *(5)*?

2) If so, is the ready dissociation of the ethane *(4)* caused by stabilization of the methyl formed owing to delocalization of the unpaired electron over the three S atoms?

3) Is the ethylene *(6)* also formed *after* dissociation of the ethane?

On catalysis by HCl (14 days' stirring at 20 °C), formic acid (60% labeled by ^{13}C; 0.50 g, 10.8 mmol) and thiophenol (3.30 ml, 33.0 mmol) gave[6] a 72% yield of labeled tris(phenylthio)methane; the NMR spectrum of its methine H is shown in Fig. 1a: $J_{^{13}C-H} = 168$ Hz, 60% of ^{13}C and 40% of ^{12}C molecules. When heated with xylene, samples of the labeled ethane *(4)* prepared from the methane[7] gave the ESR spectrum shown in Fig. 1b[8]. The relative intensities of the three lines (3:4:3) correspond to a methyl radical with 60% content of ^{13}C. The coupling constant $a_{^{13}C} = 43.69$ gauss is large[9] and so indicates that the lone electron is only slightly delocalized over the three S atoms of the tris(phenylthio)methyl. Since the appropriate π-σ-parameters are unknown it is not yet possible to determine the spin density distribution exactly[10]. The spectrum cannot be brought into accord with the paramagnetic molecule *(7)*, as is shown by a glance at the spectrum simulated[11] for this ethyl radical (Fig. 1c).

The question of how *(6)* is formed was solved by the following scrambling experiment:



unscrambled mixture — scrambled product

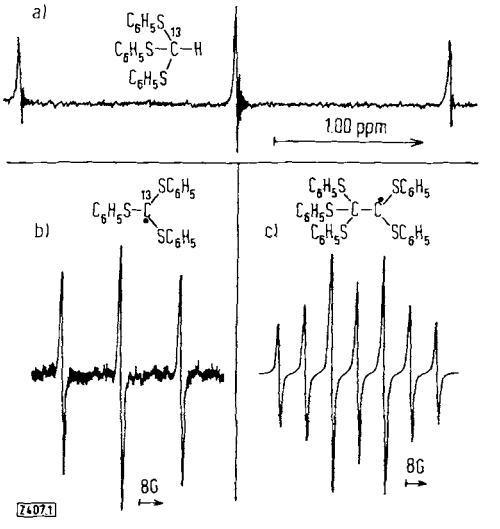


Fig. 1. (a) ^{1}H-NMR spectrum of labeled tris(phenylthio)methane. (b) ESR spectrum of labeled tris(phenylthio)methyl. (c) Simulated ESR spectrum of labeled pentakis(phenylthio)ethyl.

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If the ethylene is formed without previous dissociation of the ethane (route a), pyrolysis of a mixture of labeled and unlabeled ethane will give ethylene of isotope composition different from that obtained after a preceding dissociation (route b). The figures given in Table 1 show that complete

Table 1. ^{13}C isotope distribution, determined by mass spectroscopy and calculated, of the ethylene *(6)* formed on pyrolysis of a 1:1 mixture of labeled (60%) and unlabeled *(4)* (10 hours' refluxing in pyridine under argon).

No of ^{13}C atoms in *(6)*	Percentage distribution of masses 460, 461, 462 calculated without scrambling	calculated with scrambling	found
0	58.0	49.0	52.5
1	24.0	42.0	39.1
2	18.0	9.0	8.4

scrambling takes place. We proved in a separate experiment that no crossing between labeled and unlabeled ethylene *(6)* occurs at 250°C, and thus formation of the ethylene molecule must be preceded by homolysis of the ethane bond.

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[2] *M. Gomberg,* Ber. Dtsch. Chem. Ges. *33*, 3150 (1900).

[3] *P. Jacobson,* Ber. Dtsch. Chem. Ges. *38*, 196 (1905).

[4] *D. Seebach, A. K. Beck,* and *H. B. Stegmann,* Tetrahedron Lett. *1970*, 1933.

[5] Tris(phenylthio)methane, tetrakis(phenylthio)methane (we erroneously assigned an episulfide structure to this compound [4], being mainly deceived by fragmentation in the mass spectrometer), phenyl dithiobenzoate, and diphenyl disulfide.

[6] *B. Holmberg,* Ber. Dtsch. Chem. Ges. *40*, 1740 (1907).

[7] *D. Seebach,* Angew. Chem. *79*, 469 (1967); Angew. Chem. internat. Edit. *6*, 443 (1967).

[8] The same spectrum appears when labeled tetrakis(phenylthio)-methane is heated (cf. [4]).

[9] Measured and calculated ^{13}C coupling constants for the localized methyl radical lie in the same region: *K. Scheffler* and *H. B. Stegmann:* Elektronenspinresonanz. Springer, Berlin 1970, p. 183.

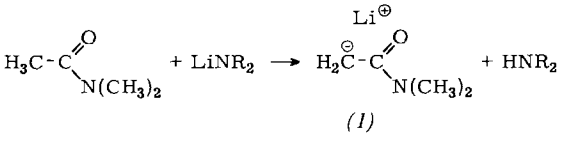
[10] The costly labeling of *(4)* with ^{33}S for determination of coupling with sulfur is planned.

[11] For the calculation we assumed the experimental α-^{13}C coupling of 43.69 gauss, a β-^{13}C coupling of 22.00 gauss [corresponding to the experimental values of *H. L. Strauss* and *G. K. Fraenkel,* J. Chem. Phys. *35*, 1738 (1961)], and a statistical distribution of the ^{13}C nuclei between the two central C atoms of *(7)*, *i.e.*, 16% without ^{13}C, 48% with one ^{13}C, and 36% with two ^{13}C. The simulation was carried out on a CDC-3300 computer at the Zentrum für Datenverarbeitung der Universität Tübingen.

Michael Addition of Metalated Carboxamides to Nitrostyrenes—A Simplified Route to Tryptamines[**]

By *Dieter Seebach* and *Herbert F. Leitz*[*]

Solutions of pure lithium *N,N*-dimethylacetamide *(1)* can be obtained by metalation of the amide with 1,3,5-trithian-2-yllithium in tetrahydrofuran (THF)[1]. It turns out that the enolate *(1)* can also be obtained[3], mixed with an equivalent of dialkylamine[2], according to the equation:



(1)

Table 1. Physical properties and yields of compounds of type *(4)* to *(6)*.

R	Nitro amides *(6)* Yield (%)	M. p. (°C)	Butanediamines of type *(4)*, *(5)* Yield (%)	M. p. (°C) [a]
4-Chloro-	94	94.4–95.3		
2-Benzyloxy-	99	92.8–94.0	79	a: 230.0–231.6
2,5-Dimethoxy-	97	106.4–107.8	76	b: 189–190 c: 200–201 [b]
5-Chloro-2-methoxy	98	118.0–119.0	72	b: 150.8–152.8 c: 184–186 [c]
2-Benzyloxy-5-chloro-	98	99.4–100.4	74	b: 176.0–177.6
2-Benzyloxy-5-bromo-	90	105.0–106.2	5 [d]	b: 184.0–185.5
2,5-Dimethoxy-4-methyl-	95	124.6–126.0	83	a: 240–242
3,4,5-Trimethoxy-	78	109.0–110.3	74	a: 246–247 b: 167.8–169.0

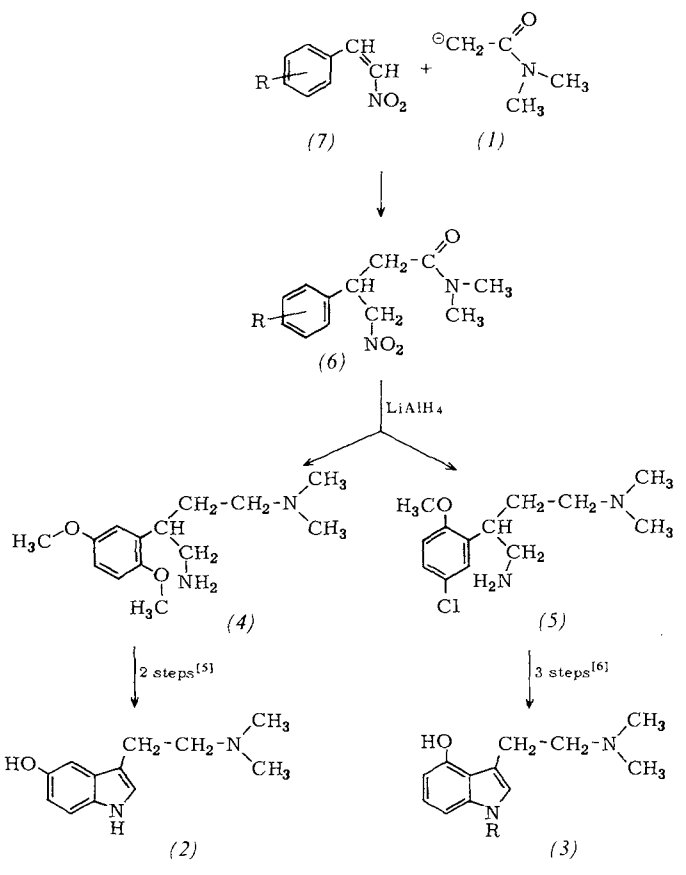
[a] a: Dihydrochloride. b: Bis(hydrogen oxalate). c: Dipicrate. The salts melt with decomposition, particularly the oxalates and picrates.
[b] Lit. [5]: 198—199°C; see formula *(4)*.
[c] Lit. [6]: 186°C; see formula *(5)*.
[d] Debromination occurs on reduction; this amine is obtained in 81% yield by bromination of the benzyloxy amine (second row in the above Table) in glacial acetic acid containing sodium acetate [10].

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The amine does not interfere in many of the reactions of *(1)*, the use of which for elaboration of indole alkaloids is reported here.

The hallucinogens bufotenine *(2)* and psilocine and its derivatives *(3)*, which are of interest as psychomimetic drugs[4] in psychiatry, can be synthesized from the precursors *(4)* (by oxidative ring closure[5]) and *(5)* (by aryne ring closure[6, 7a]) respectively; however, preparation of *(4)* and *(5)* is cumbersome[5, 6, 7b], and other methods (*Fischer-Bischler*, *Reissert*, and *Speeter-Anthony*) of preparing *(2)* and especially *(3)* and similar tryptamines require many steps[4–6, 7b].



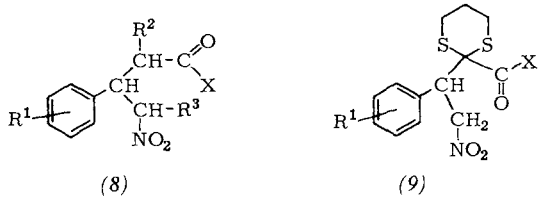
We have found that one arrives at the skeleton of compounds *(4)* and *(5)* by the following route: Addition of *(1)* to nitrostyrenes *(7)*[8] affords[3, 9] almost quantitative yields (Table 1) of the nitro amides *(6)*, whose reduction by lithium tetrahydridoaluminate leads directly to the 2-aryl-1,4-butanediamines (Table 1). The structures of the adducts *(6)* and the amines obtained from them are proved by elemental analyses and spectroscopic properties.

The synthesis is variable: Not only may the benzene ring contain different types of sensitive substituents ($OCH_2C_6H_5$, Cl, Br) (Table 1), but also the dimethylacetamide may be replaced by diethylacetamide [→*(8a)*], dimethylpropionamide [→*(8b)*], 1,3-dithiane-2-carboxamide [→*(9)*], or ethyl acetate [→*(8c)*], and the nitrostyrenes *(7)* by nitrophenylpropenes [→*(8d)*] (Table 2).

Table 2. Physical properties and yields of compounds *(8)* and *(9)*.

	R^1	R^2	R^3	X	Yield (%)	M.p. (°C)
(8a)	2,5-Dimethoxy-4-methyl-	H	H	$N(C_2H_5)_2$	85	76.4–77.6
(8b)	2-Benzyloxy-	CH_3	H	$N(CH_3)_2$	95	83–101 [a]
(8c)	3,4,5-Trimethoxy-	H	H	OC_2H_5	94	90–92
(8d)	2,5-Dimethoxy-4-methyl-	H	CH_3	$N(CH_3)_2$	71	75–85 [a]
(9a)	2,5-Dimethoxy-4-methyl-			$N(CH_3)_2$	88	136.8–137.8
(9b)	2,5-Dimethoxy-4-methyl-			$N(CH_2)_4$	87	120.5–121.7
(9c)	3,4,5-Trimethoxy-			$N(CH_2)_4$	83	140.4–144.0

[a] Diastereoisomeric mixture according to the NMR spectrum.



Experimental:

3-[*o*-(Benzyloxy)phenyl]-*N*,*N*-dimethyl-4-nitrobutyramide *(6)* (R = *o*-benzyloxy): *N*,*N*-Dimethylacetamide (75 mmol) is added to a solution of lithium diisobutylamide (from the amine and butyllithium) (60 mmol) in THF (100 ml) and hexane (25 ml) under argon at −78 °C. After 1 h, *o*-

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[2] Diisopropyl- or diisobutyl-amine was used [3].

[3] See experimental.

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[5] *L. Harley-Mason* and *A. H. Jackson*, J. Chem. Soc. *1954*, 1165.

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[7] a) *R. W. Hoffmann*: Dehydrobenzene and Cycloalkynes. Verlag Chemie, Weinheim 1967, Chap. 2,3. b) *R. J. Sundberg*: The Chemistry of Indoles. Academic Press, New York 1970.

[8] Readily prepared from the corresponding substituted aldehydes and nitroalkanes; for recent examples see: *B. T. Ho et al.*, J. Med. Chem. *13*, 134 (1970); see also Houben-Weyl, Methoden der Org. Chemie, Vol. X/1, p. 336ff, Thieme Verlag, Stuttgart 1971.

[9] Cf. *D. Seebach* and *H. F. Leitz*, Angew. Chem. *81*, 1047 (1969); Angew. Chem. internat. Edit. *8*, 983 (1969).

[10] For procedure cf.: *L. C. Raiford* and *L. K. Tanzer*, J. Org. Chem. *6*, 722 (1941).

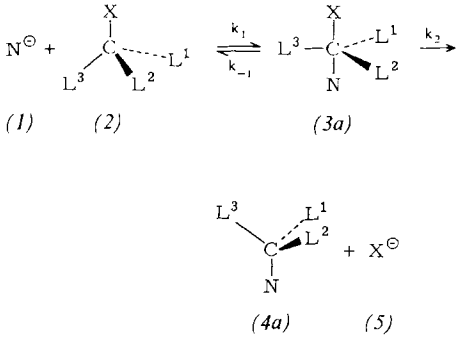
(benzyloxy)-1-nitrostyrene *(7)* (R = *o*-benzyloxy) (50 mmol), dissolved in THF (100 ml) is added dropwise with vigorous stirring during 50 min, and the mixture is stirred for a further 2 h at −78 °C and then treated at this temperature with glacial acetic acid (15 ml). The colorless solution is allowed to warm to 20 °C, H_2O (60 ml) is added, and the solvents are removed in a rotary evaporator. The crystalline product is filtered from the residue, washed with H_2O, and dried. Yield 16.9 g, 99%; m. p. 90.1—92.0 °C; m. p. of analytical sample (from ethanol-pentane) 92.8 to 94 °C; NMR spectrum (in $CDCl_3$): 9 aromatic hydrogens as multiplet at $\tau = 2.5—3.3$, benzylic CH_2 as singlet at $\tau = 4.98$; α-nitro-CH_2 as doublet (6.7 Hz) at $\tau = 5.17$; benzylic CH as doublet (6.7 Hz) of doublets (6.5 Hz) at $\tau = 5.70$; *N*-methyls as two singlets at $\tau = 7.30$ and 7.24; α-carbonyl-CH_2 as doublet (6.5 Hz) at $\tau = 7.30$.

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A Reexamination of the Limiting Mechanisms of Aliphatic Nucleophilic Substitution

By *Paul D. Gillespie* and *Ivar Ugi*[*]

The limiting mechanisms concerning aliphatic nucleophilic substitution reactions introduced by *Ingold* and co-workers have been a part of the basic textbook knowledge of organic chemists for three decades[1]. These ideas have served the chemist well as a model for mechanistic thought and have provided reliable interpretations of and predictions for many reactions. Doubt no longer exists concerning the intermediacy of carbonium ions with tricoordinate carbon[2] in an S_N1 elimination addition mechanism. However, the questioning has never ceased regarding the nature of the pentacoordinate carbon species *(3a)* involved during the limiting S_N2 and S_Ni process[3-10].

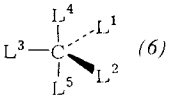


(1) *(2)* *(3a)* *(4a)* *(5)*

Scheme 1. N = nucleophile, L = ligand.

Experimental evidence supporting the presently accepted S_N2 concept is primarily kinetic and stereochemical in nature[1,5,6,11]. Second order kinetics have established that both reacting species *(1)* and *(2)* participate in formation of the transition state for the rate-determining step and the well-known stereochemistry of Walden inversion have contributed to the supposition that the trigonal-bipyramidal carbon species *(3)* with apical entering and leaving groups is a transition state in the reaction (Scheme 1)[11,12].

The assumption that *(3a)* must be a transition state and not an intermediate was due to the natural aversion to presume any stability in a pentacoordinate carbon compound[1,11]. However, some authors have pointed out that intermediates corresponding to a well in the potential energy surface might be formed in the course of S_N2 reactions[2b,4-6]. Recently, several examples of relatively stable pentacoordinate carbon compounds, $CH_5^{\oplus}$[2], $CCl_5^{\ominus}$[13], and $CBr_5^{\ominus}$[14], as well as theoretical work yielding stability estimates for the model systems $CH_5^{\ominus}$[7-10] and $CH_3F_2^{\ominus}$[9] have appeared in the literature. The latter information combined with recent experimental and theoretical investigations on pentacoordinate molecules[15a,b] and their role during chemical reactions[15c] stimulated us to reexamine the mechanistic concepts upon which the interpretation of nucleophilic substitution on saturated carbon is based.



(6)

Table 1 contains binding energy (BE) data, obtained by the use of the CNDO/2[17] approximation, for pentacoordinate carbon compounds *(6)* with a trigonal-bipyramidal skeletal structure. The various isomers, not treated in prior calculations[9], are included for each compound.

Table 1. Equilibrium geometry binding energies (BE) of Walden species and their permutation isomers [16].

Cpd.	Ligands and bond lengths C—L (L^1—L^5) (Å) equatorial			apical		BE (kcal/mole)
(6a)	H	H	H	F	F	−969.4
	1.160	1.160	1.160	1.440	1.440	
($6a_1$)	H	H	H	F	F	−967.9
	1.160	1.160	1.160	1.450	1.450	
($6a_2$)	H	H	H	F	F	−968.9
	1.160	1.160	1.160	1.430	1.430	
($6a_3$)	H	H	H	F	F	−969.2
	1.160	1.160	1.160	1.450	1.430	
($6a_4$)	H	H	H	F	F	−967.5
	1.160	1.160	1.160	1.470	1.420	
(6b)	H	H	F	H	F	−993.8
	1.150	1.150	1.380	1.170	1.410	
($6c_1$)	H	F	F	H	H	−989.0
	1.150	1.380	1.380	1.200	1.200	
($6d_1$)	H	H	H	OH	F	−1137.9
	1.160	1.160	1.160	1.460	1.440	
($6e_1$)	H	H	OH	H	F	−1167.8
	1.150	1.150	1.400	1.170	1.440	
(6f)	H	H	F	H	OH	−1160.9
	1.450	1.150	1.410	1.170	1.440	
(6g)	H	OH	F	H	H	−1164.6
	1.150	1.405	1.380	1.200	1.200	
(6h)	H	H	H	CN	F	−1632.9
	1.170	1.170	1.170	1.500	1.450	
(6i)	H	H	CN	H	F	−1662.9
	1.150	1.150	1.470	1.170	1.450	
(6j)	H	H	F	H	CN	−1652.1
	1.150	1.150	1.400	1.170	1.480	
(6k)	H	CN	F	H	H	−1663.4
	1.150	1.450	1.390	1.200	1.200	

The BE of *(6a)* as a function of the C—F bond distance shows that any small displacement of the F ligands from their equilibrium position (similarly for the H ligands) leads to an increase in the energy of the "Walden species" [see *($6a_1$)—($6a_4$)], *i.e.*, it can be stated that *(6a)*

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corresponds to a local minimum in the potential surface and, by definition, is an *intermediate*, not a transition state. This holds for the other model species *(6b)*—*(6k)* of Table 1 as well. Approximations contained in the CNDO/2 method and the neglect of zero point energies are not critical for establishing the intermediate nature of these species and presumably for the qualitative comparison between the BE for the permutation isomers in Table 1. *Berthier, David,* and *Veillard*[9a] found that the potential energy of the "Walden species" *(6a)* is lower than that of $CH_3F+F^{\ominus}$, which may be due to neglected differences in zero point energies[17] of *(6a)* and the latter. These differences become important when either the number or type of bonds or ligands change.

BE comparison between isomers *(6a)*—*(6c)*, *(6d)*—*(6g)*, and *(6h)*—*(6k)* indicate that the polarity rule[15c] does not seem to hold for pentacoordinate carbon compounds; in fact the opposite seems to be true[*]. This phenomenon may be due, in part, to the fact that the ligands are required to carry more electron density than they would in some neutral species, combined with the fact that the hydrogens carry the majority of the excess charge since fluorine already enters with a negative charge. Further, lack of d orbitals in the basis set eliminates a pathway for electron density to be passed back to the carbon atom in these model calculations. This results in the highly negatively charged hydrogen atoms seeking apical sites in an effort to avoid each other. Such relative stabilities of the permutation isomers of the trigonal-bipyramidal system, though, do not cause difficulties for understanding the steric course of the S_N2 and S_Ni reactions (see below).

There are two types of limiting bimolecular mechanisms, S_N2 and S_Ni, for S_N processes at a saturated C-atom which proceed *via* a pentacoordinate intermediate *(6)* with a trigonal-bipyramidal molecular skeleton as addition-elimination processes accompanied by a change in coordination number of carbon: 4→5→4. For both of these types of bimolecular S_N processes the transformation of the tetracoordinate C-compound into the pentacoordinate species results from an *attack on any face* [see *(3a)*—*(3d)*] of the tetrahedron by the nucleophile such that the entering group assumes an apical position in the intermediate. The latter decomposes by apical departure of the leaving group. Recently, the necessity for *apical entry and departure* has been confirmed in an elegant manner by *Eschenmoser et al.*[18]. Their experiments demonstrate that if the steric requirements for both apical entry and departure are not fulfilled, no nucleophilic substitution *via* pentacoordinate species takes place. Observations from these experiments are well in accord with the concepts developed in this and preceding papers[15] and in particular with the properties of cyclic pentacoordinate species with three- to five-membered rings *vs.* those with six-membered rings.

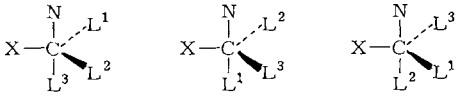
Scheme 1 illustrates a process corresponding to the classical S_N2 mechanism except that *(3a)* is an *intermediate*, not a transition state. Since pentacoordinate carbon compounds with the more electronegative ligands

[*] *Note added in proof* (May 28, 1971):
The polarity rule [15c] seems to apply only in systems where substantial d orbital participation exists. We are led to this position as a result of recently completed BE comparisons between the various isomers of PH_3F_2 and PH_2F_3 calculated in one case employing d orbitals in the CNDO/2 basis set and in another case without. While the former set of data shows clearly that these systems comply with the polarity rule, the latter data set indicates that this rule does not hold, leading one to believe hybridization changes in the bond system weigh heavily in determining ligand positions on a molecular skeleton.

Table 2. Bond orders, β values and valence shell electron populations for *(6a)* and *(6b)*. Diagonal elements on C are orbital electron populations. Italic entries are the bond orders while the first entry in each column is a core energy term whose negative product with the bond order represents the orbital contribution to the eletronic energy. The *z*-axis is the apical direction, the *x*-axis is in the equatorial plane with C—H(13) the $+x$ direction.

Orbitals		*(6a)*				*(6b)*				*(6a)*	*(6b)*
		1	2	3	4	1	2	3	4	$\sum e^-$	$\sum e^-$
1	C2s	0.9784				0.9533					
2	$C2p_x$		0.8920				0.8528			3.4842	3.3870
3	$C2p_y$			0.8920				0.7847			
4	$C2p_z$				0.7218				0.7962		
5	F2s	−0.2462			−0.3477	−0.2594			−0.3638		
		0.1187			*0.3247*	*0.1596*			*0.3381*		
6	$F2p_x$		−0.1162				−0.1245				
			0.1245				*0.1326*			7.5006	7.4406
7	$F2p_y$			−0.1162				−0.1245			
				0.1245				*0.1479*			
8	$F2p_z$	0.2092			0.2694	0.2179			0.2768		
		−0.3142			*−0.5965*	*−0.3552*			*−0.6153*		
9	F2s				0.3477	−0.2731	0.1901	0.3292			
					−0.3247	*0.1762*	*−0.1916*	*−0.3319*			
10	$F2p_x$		−0.1162			−0.1133		0.1806			
			0.1245			*0.1803*		*−0.3733*		7.5006	7.3425
11	$F2p_y$			−0.1162		−0.1963	0.1806	0.1794			
				0.1245		*0.3123*	*−0.3733*	*−0.4735*			
12	$F2p_z$	−0.2092			0.2694				−0.1333		
		0.3144			*−0.5965*				*0.1288*		
13	H1s	−0.2648	−0.2570			−0.2678	−0.2588			1.1715	1.2225
		0.5078	*0.7989*			*0.4764*	*0.7826*				
14	H1s	−0.2648	0.1285	−0.2225		−0.2678	0.1294	−0.2241		1.1715	1.2225
		0.5078	*−0.3994*	*0.6919*		*0.4764*	*−0.4059*	*0.6693*			
15	H1s	−0.2648	0.1285	0.2225		−0.2618			0.2551	1.1715	1.3849
		0.5078	*−0.3994*	*−0.6919*		*0.4676*			*−0.6650*		

in the equatorial plane are preferred, the formation of a methane derivative *(4)* not only from *(3a)* but from the isomers *(3b)*—*(3d)* as well is to be expected.



(3b) *(3c)* *(3d)*

Although formation of the latter three intermediates may be favored over that of *(3a)*, they do not lead to a substitution process by apical departure if none of the ligands L^1 to L^3 has sufficient leaving properties unless reorganization by BPR or TR processes[15] (BPR = Berry pseudorotation, TR = turnstile rotation) forms intermediates with an apical leaving group. BPR and TR processes always transform *(3b)*—*(3d)* into such pentacoordinate molecules which by apical departure of X lead to *(4b)*, *i.e.*, configuration retention (corresponding to an S_Ni process).

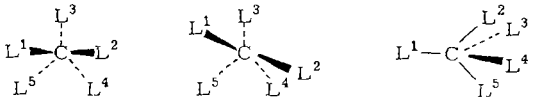


(4b) *(3e)*

Double TR processes[15] in *(3b)*—*(3d)* yield the inversion product *(4a)* upon decay of the trigonal-bipyramidal intermediate if N and X simultaneously belong to the trio of the double TR process, and yield *(4b)* by all other double TR processes. Furthermore, *(3a)* can also undergo BPR or TR reorganization to give *(4a)* and *(4b)*, *e.g.*, *via (3e)*.

It appears that the generally observed inversion of configuration resulting from bimolecular nucleophilic substitution on saturated carbon is due to the fact that rearrangement processes required for retention lead to energetically disfavored trigonal-bipyramidal isomers and have, in general, relatively high potential energy barriers. They therefore occur more slowly than the elimination of apical ligands of pentacoordinate intermediate *(3)*.

Table 3 contains the BE data of some BPR and TR barrier models of *(3a)*⇄*(3b)* and *(3b)*⇄*(3c)*. One can determine, by comparing the BE of certain BPR and TR transition states with the BE of the parent trigonal bipyramid, that



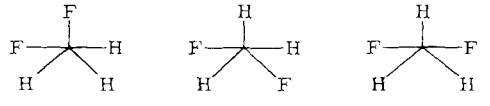
(7) *(8)* *(9)*

the energy barrier for positional exchange is less than 10 kcal/mole on the average, far less than the barriers predicted by earlier calculations[7,8].

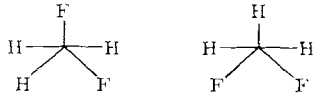
Since pentacoordinate molecules with a trigonal-bipyramidal skeleton possessing diequatorial three- to five-membered rings are far more strained than the corresponding apical-equatorial analogs[15c], one can expect, assuming apical entry and departure, that bimolecular S_N processes of three- to five-membered cyclic systems will not proceed exclusively with inversion but predominately with retention.

Table 3. BE data of the conceivable barrier situations *(7)*, *(8)*, and *(9)* for positional exchange in $CH_3F_2^{\ominus}$ trigonal-bipyramidal species of the kind *(3a)*⇄*(3b)* and *(3b)*⇄*(3c)*. Figures under formulas are in kcal/mole.

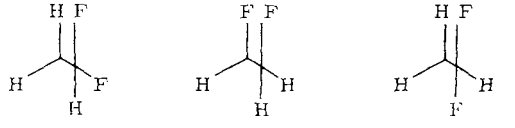
Cpd.	L^1	L^2	L^3	L^4	L^5	∢ L^1—C—L^2 (°)	∢ L^3—C—L^5 (°)
	C—L distance (Å)						
	H	F	F	H	H		
(7)	1.17	1.41	1.40	1.16	1.16	85	95
(8)	1.17	1.41	1.40	1.16	1.16	85	95
(9)	1.17	1.41	1.41	1.16	1.16	105	86



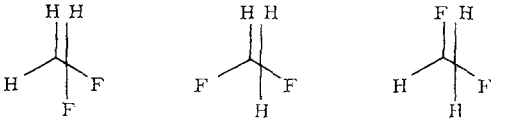
(7a) -973.9 *(7b)* -979.7 *(7c)* -977.9



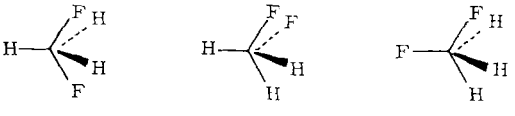
(7d) -979.9 *(7e)* -978.5



(8a) -978.6 *(8b)* -978.4 *(8c)* -977.9

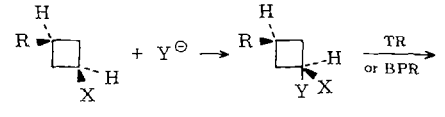


(8d) -979.6 *(8c)* -981.2 *(8f)* -977.3

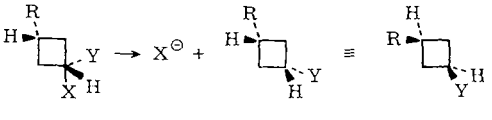


(9a) -965.1 *(9b)* -985.5 *(9c)* -984.0

If a cyclobutane derivative *(10)* undergoes a nucleophilic substitution under conditions where the bimolecular S_N2 process is faster than the S_N1 (which would lead to a detectable carbonium ion rearrangement[11]), we are led to expect an S_N process with configurational retention



(10) *(11)*



(12a) *(13a)*

[(10)→(13)]. Since diequatorial three- to five-membered rings are energetically disfavored in trigonal-bipyramidal molecules[5] apical attack by $Y^{\ominus}$ on (10) can only lead to (11); apical departure of $X^{\ominus}$ is only possible after a rearrangement (11)→(12) which is favored if $X^{\ominus}$ prefers apical and $Y^{\ominus}$ equatorial placement on the trigonal-bipyramidal skeleton.

The acceleration of bimolecular S_N processes by substituents, *e.g.*, CN, R—CO, and probably RO, is due to the stabilization of the trigonal-bipyramidal intermediates by those groups, particularly in equatorial positions, and to a lowering of the activation energy for their formation [$k(S_N2)=k_1k_2/k_{-1}+k_2\approx k_1$, if $k_2 \gg k_{-1}$, see Scheme 1].

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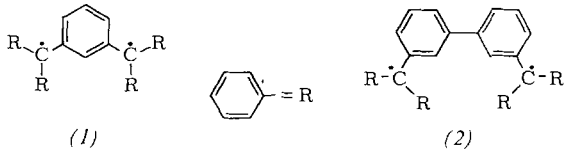
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The Energetic Positions of the Lowest Singlet and Triplet State of the Schlenk and of the Müller Hydrocarbon

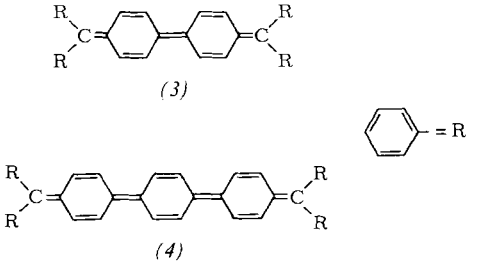
By *Reinhard Schmidt* and *Hans-Dieter Brauer*[*]

π-Electron systems with an even number of centers and π-electrons, in which in the HMO approximation the two highest occupied HMO's are mutually degenerate, usually occupy a triplet ground state[1,2]. This is also the case, according to more recent work, for the Schlenk hydrocarbon (1)[2,3], but according to *Hückel*[4] the Schlenk hydrocarbon (2) could provide an exception to this rule. Specifically, Hückel estimates that in this case the exchange integral which determines the splitting of corresponding singlet and triplet states is very small, and within the accuracy of the approximation procedure the same energy is obtained for the lowest singlet and triplet state of (2). Accordingly, (2) should possess a biradical ground state and should behave like a "doubled" triphenylmethyl radical[5].



(1) (2)

According to classical valence theory the occurrence of two unpaired electrons in the ground state of compounds (1) and (2) is to be regarded as a consequence of the non-existence of *m*-quinonoid systems, which makes it impossible to compensate the valences in the two halves of the molecules (1) and (2). The situation is quite different when the topology of the system permits intramolecular valence compensation; for example, the Chichibabin hydrocarbon (3), which is isomeric with (2), should, if the atoms lie in one plane, possess a singlet ground state, since the highest occupied HMO is not degenerate[1,4], and this follows both from the standpoint of classical valence theory and from HMO theory; this accords with experience. However, the lowest triplet state of (3) is energetically so low that it is excited even at moderate temperatures. According to ESR spectroscopic investigations of the solid substance the energy difference ΔE between the lowest triplet and singlet ground state of planar (3) is about 5.5 ± 1.0 kcal/mol[6]; and according to *Seel*'s quantum-theoretical calculations[7] a still smaller energy difference ΔE is to be expected for the Müller hydrocarbon (4).



(3) (4)

To discover whether the theoretical ideas concerning the positions of the lowest singlet and triplet states of (2) and (4) are correct, ESR spectroscopic measurements have been carried out with these compounds.

The hydrocarbons (2) and (4) were synthesized according to the publication of *Schlenk* and *Brauns*[8] and of *Müller* and *Pfanz*[9], respectively. To demonstrate molecules in the triplet state, a 0.5% solutions of (2) and a 0.1% solution of (4) in toluene under very pure nitrogen were studied at low temperatures; to avoid complete association, the solutions were heated for a short time at 60°C and then rapidly cooled in liquid nitrogen.

Figure 1 shows the ESR spectrum of the rigid glassy toluene solution of (2) at −120°C; it contains several signals

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($\Delta m = 1$) characteristic of triplet molecules as well as a very intense $^2\Sigma_{1/2}$ signal at 3260 G; we ascribe the triplet spectrum to monomeric *(2)*. The values of the zero field splitting parameters[10] calculated from the ($\Delta m = 1$) transitions are $|D| = 0.0049\ cm^{-1}$, $|E| \leq 0.0003\ cm^{-1}$. A triplet molecule was also detected for *(4)*; the ESR spectrum of the glassy solidified toluene solution of *(4)* at −120 °C is

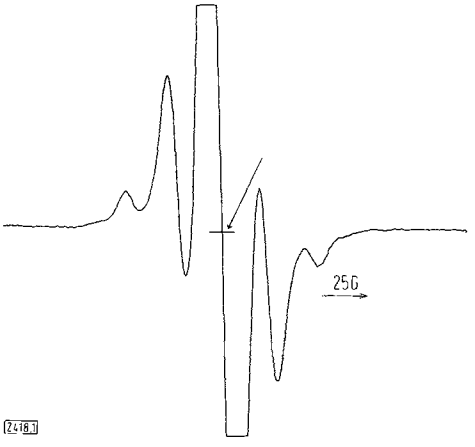


Fig. 1. ESR spectrum of 3,3'-bis(diphenylmethyl)biphenyl *(2)* in glassy solidified toluene at −120 °C. Arrow: 3260 G.

analogous to that of the compound *(2)*; the values obtained for the zero field splitting parameters amount to $|D| = 0.0035\ cm^{-1}$, $|E| \leq 0.0002\ cm^{-1}$. (The zero field splitting parameters of both hydrocarbons are slightly temperature-dependent.) The ($\Delta m = 2$) absorption signal could not be observed for either hydrocarbon.

To answer the question whether the triplet molecules demonstrated for *(2)* and *(4)* are molecules in the triplet ground state or thermally excited molecules in the lowest triplet state, we have measured the temperature-dependence of the ($\Delta m = 1$) signals over the range 153–183 °K; this was evaluated from the relation (1)[11]:

$$I = \frac{C}{T} \frac{3 \cdot e^{-\Delta E/RT}}{1 + 3 \cdot e^{-\Delta E/RT}} \qquad (1)$$

$\Delta E = E_{triplet} - E_{singlet}$, C = constant

Calculations by eqn. (1) from the variation of signal amplitudes with temperature afford for *(2)* a value of ΔE of -0.3 ± 0.15 kcal/mol and for *(4)* a value of ΔE of 0.9 ± 0.3 kcal/mol.

From these investigations it follows that the hydrocarbon *(2)* has a triplet ground state and not a biradical ground state as would appear possible by *Hückel*'s calculations. According to our measurements the triplet ground state, however, is only about 0.3 kcal/mol more stable than the lowest singlet state. On the other hand, as predicted by theory, the Müller hydrocarbon *(4)* has a singlet ground state; the excitation energy of about 1 kcal/mol found for the lowest triplet state is in accord with expectations from theory[7].

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Synthesis of (Isothiocyanatoacyl)amino Acids

By *Hans R. Kricheldorf*[*]

N-(Isothiocyanatoacyl)amino acids *(1)* are crystalline compounds that are stable at room temperature and, like isothiocyanato carboxylic acids[1], can be condensed to polypeptides or polyamides *(2)* with loss of COS at elevated temperatures or in presence of catalysts.

$$n\ S{=}C{=}N\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}COOH \quad (1)$$

$$\downarrow -(n-1)\ COS$$

$$S{=}C{=}N\text{-}A\text{-}CO\text{-}[\text{-}NH\text{-}B\text{-}CO\text{-}NH\text{-}A\text{-}CO]_{n-1}\text{-}OH \quad (2)$$

The monomers *(1)* can be synthesized by either of two methods, according to the availability of the starting material:

1. An amino acid in a suitable solvent mixture is converted by the stoichiometric quantity of chlorotrimethylsilane into the trimethylsilyl ester hydrochloride *(3)*[2], which is then acylated by an isothiocyanato carbonyl chloride; the resulting trimethylsilyl *N*-(isothiocyanatoacyl)amino esters *(4)* can be hydrolyzed to the monomers *(1)* by water (or alcohol) rapidly and under mild conditions.

$$\overset{\oplus}{N}H_3\text{-}B\text{-}COO^{\ominus} + (CH_3)_3SiCl \rightarrow \overset{\ominus}{Cl}[\overset{\oplus}{N}H_3\text{-}B\text{-}CO\text{-}OSi(CH_3)_3] \quad (3)$$

$$(3) + SCN\text{-}A\text{-}CO\text{-}Cl \xrightarrow[-2R_3N \cdot HCl]{+2R_3N}$$

$$SCN\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}CO\text{-}OSi(CH_3)_3 \quad (4)$$

2. A dipeptide is converted analogously into the trimethylsilyl ester hydrochloride, and the latter is treated with carbon disulfide and triethylamine, giving the dithiocarbamate *(5)*. Acylation with a chloroformic ester below 0 °C affords the *N*-[(alkoxycarbonylthio)thiocarbonyl]-dipeptide trimethylsilyl ester *(6)*, which can be hydrolyzed to the crystalline acid *(7)* that is thus easily purified and can also be polycondensed. Silylation of *(6)* or *(7)* affords the silyl esters *(4)*.

Both methods can be carried out in one operation and are also suitable for preparation of isothiocyanato oligopeptides.

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$$\ominus\oplus Cl[NH_3\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}CO\text{-}OSi(CH_3)_3] + CS_2 + 2\ R_3N$$

$$\rightarrow R_3\overset{\oplus}{N}H[\overset{\ominus}{S}CS\text{-}NH\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}CO\text{-}OSi(CH_3)_3] \quad (5)$$

$$+\ R_3N\cdot HCl$$

$$(5) + R^1O\text{-}CO\text{-}Cl \xrightarrow{-R_3N\cdot HCl}$$

$$R^1O\text{-}CO\text{-}S\text{-}CS\text{-}NH\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}CO\text{-}OSi(CH_3)_3 \quad (6)$$

$$\downarrow$$

$$R^1O\text{-}CO\text{-}S\text{-}CS\text{-}NH\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}COOH \quad (7)$$

$$(6)\ [\text{or } (7)] \xrightarrow[-R_3N\cdot HCl]{+(CH_3)_3SiCl/R_3N} (4) + R^1O\text{-}Si(CH_3)_3 + COS$$

On treatment of glycylglycine by method 2 it was found that the acids *(7)*[4] were stable, but not the *N*-(α-isothiocyanatoacyl)amino acids *(8)* since the latter cyclize even at 0 °C to thiohydantoins *(9)*.

$$SCN\text{-}A\text{-}CO\text{-}NH\text{-}B\text{-}COOH \xrightarrow{0\,^\circ C} \begin{matrix} A\text{-}CO \\ | \quad \diagdown \\ HN\text{-}CS \end{matrix} N\text{-}B\text{-}COOH$$

(8) *(9)*

Experimental:

1. An amino acid (0.3 mol) in a mixture of acetonitrile (100 ml) and anhydrous chloroform (400 ml) is heated with chlorotrimethylsilane (0.3 mol) at the boiling point for *ca.* 2 h, to give a clear solution or a suspension of the trimethylsilyl ester hydrochloride. An isothiocyanato carbonyl chloride (0.3 mol) and finally triethylamine (61 g, 0.6 mol) are added dropwise to the product at −20 °C. After 60 min the mixture is extracted with dilute citric acid solution (300 ml), and the organic phase is dried and evaporated *in vacuo*, whereupon the product usually separates in crystalline form.

2. A solution or suspension of a dipeptide trimethylsilyl ester hydrochloride, prepared as in method 1, is stirred at room temperature with carbon disulfide (24 g, 0.3 mol) and triethylamine (61 g, 0.6 mol) for 4 h. Then an alkyl chloroformate (0.3 mol) is added dropwise while the temperature is not allowed to rise above 0 °C. After 30 min, a solution of chlorotrimethylsilane (40 ml) in anhydrous chloroform (250 ml) and triethylamine (42 ml, 0.3 mol) are dropped in, then the mixture is stirred for a further hour at room temperature and finally worked up as in method 1.

The IR spectra of the compounds named in the title show three characteristic bands: at 4.7 to 4.8 μm (2100 cm^{-1}; isothiocyanate group), 5.8 to 5.9 μm (1700 cm^{-1}, carboxyl group), and 6.1 μm (1640 cm^{-1}, amide-carbonyl).—*N*-(3-Isothiocyanatopropionyl)-β-alanine, m.p. 75–77 °C; *m*-*N*-(3-isothiocyanatopropionyl)aminobenzoic acid, m.p. 158 to 160 °C; *N*-(6-isothiocyanatohexanoyl)-DL-alanine, n_D^{20} = 1.5288, m.p. 43–46 °C.

The results of C—H and N elemental analyses agree with the theoretical values within ±0.3%.

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Synthesis of Dithiophosphinic Acids by Nucleophilic Fission of Perthiophosphonic Anhydrides

By *Klaus Diemert* and *Wilhelm Kuchen*[*]

Dithiophosphinic acids $R_2P(S)SH$ and their salts are of interest as excellent complexing agents and also as intermediates in the synthesis of organophosphorus compounds[1, 2].

We have found that these acids can be prepared conveniently by nucleophilic fission of the readily accessible perthiophosphonic anhydrides *(1)*[3, 4] with Grignard reagents.

$$\begin{matrix} S & S \\ \| & \| \\ RP\text{-}S & PR \\ \quad\diagdown & \diagup \\ \quad\ S & \end{matrix} \xrightarrow[H^\oplus/H_2O]{2\ R'MgX} 2\ \begin{matrix} R & S \\ \diagdown & \| \\ & P \\ \diagup & \diagdown \\ R' & SH \end{matrix}$$

(1)

The resulting acids are isolated, some as such, and some as their salts or Ni(II) complexes. We prepared the compounds listed in Table 1.

The process is especially useful for synthesis of acids containing different substituents R, and also for preparation of bisdithiophosphinic acids *(2)* (previously difficult of access) by use of bifunctional Grignard reagents

$$\begin{matrix} R & & R \\ | & & | \\ HS\text{-}P\text{-}R''\text{-}P\text{-}SH \\ \| & & \| \\ S & & S \end{matrix}$$

(2)

XMg—R″—MgX. In this way we obtained the bifunctional acid *(3)*, m.p. 149 °C ($\delta^{31}P = -50.0$ ppm), in 94% yield.

$$\begin{matrix} H_3C & & CH_3 \\ | & & | \\ XS\text{-}P & \langle\rangle & P\text{-}SX \\ \| & & \| \\ S & & S \end{matrix}$$

(3), X = H
(4), X = Na
(5), X = CH_3
(6), X = $HN(CH_3)_3$

Neutralization of *(3)* afforded the Na_2 salt *(4)*, $\delta^{31}P = -107.1$ ppm, as a fine, colorless, crystalline powder, decomp. >300 °C, which, when warmed with methyl iodide in dioxane, gave the diester *(5)*, $\delta^{31}P = -58.1$ ppm, m.p. 128–132 °C. Compound *(6)* was obtained as colorless crystals, m.p. 249 °C, by reaction of *(3)* with trimethylamine in benzene.

Experimental:

p-Methoxyphenyldithiophosphonic anhydride[4] (22.0 g, 0.054 mol), suspended in diethyl ether (220 ml), was stirred and cooled in ice while a 1M ethereal solution (120 ml, 0.12 mmol) of CH_3MgCl was added. The mixture was heated at the b.p. for 1 h, then cooled and hydrolyzed with 5% H_2SO_4 (200 ml). The ethereal layer was separated, the

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aqueous phase was extracted several times with ether, and the combined ethereal layers were dried over Na_2SO_4 and evaporated in a vacuum. The oily residue solidified after some hours to well-formed crystals that were filtered off and dried in a vacuum. This gave *p*-(methoxyphenyl)-methyldithiophosphinic acid, $(p\text{-}CH_3OC_6H_4)CH_3P(S)SH$, in 70.3% yield (16.6 g).

Table 1. Compounds of the type RR'P(S)SX synthesized.

R	R'	X	M.p. (°C)	Yield (%)	$\delta^{31}P$ (±1 ppm) [a]
CH_3	C_2H_5	Ni/2	193	25	
CH_3	C_6H_5	NH_4^+	161–163 (Lit. 161 [5])	83	−54.9
CH_3	C_6H_5	Ni/2	203–205 (Lit. 203–206 [5])	70	
CH_3	Allyl	Ni/2	150.5–154.5	55	−85.3
$p\text{-}CH_3OC_6H_4$	CH_3	H	68	70	−50.3
$p\text{-}CH_3OC_6H_4$	CH_3	$Na \cdot 2\,H_2O$	255	64	
$p\text{-}CH_3OC_6H_4$	CH_3	Ni/2	185	95	
$p\text{-}CH_3OC_6H_4$	C_2H_5	Ni/2	134	95	−88.3
$p\text{-}CH_3OC_6H_4$	C_6H_5	$HN(CH_3)_3$	147.5	70	
$p\text{-}CH_3OC_6H_4$	C_6H_5	Ni/2	234	77	
$p\text{-}CH_3OC_6H_4$	Allyl	$NH(CH_3)_3$	93	62	−60.8
$p\text{-}CH_3OC_6H_4$	Allyl	Ni/2	96.5	52	−81.2

[a] Relative to aqueous 85% H_3PO_4.

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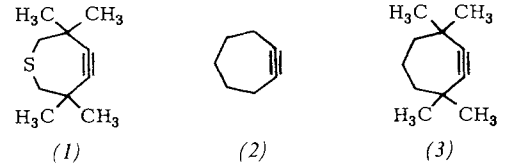
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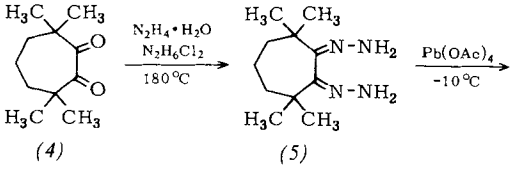
3,3,7,7-Tetramethylcycloheptyne, an Isolable Seven-Membered Carbocyclic Alkyne[1][**]

By *Adolph Krebs* and *Horst Kimling*[*]

3,3,6,6-Tetramethyl-1-thia-4-cycloheptyne *(1)* is a thermally stable compound, which shows no tendency to dimerize or oligomerize even at 140°C[2]. In contrast to *(1)*, cycloheptyne *(2)* could not be isolated—it has a half-life in 0.016 M CH_2Cl_2 solution of less than a minute at −25°C and of about an hour at −76°C[3]. We therefore posed ourselves the question whether introducing two geminal CH_3 groups at each α-position to the triple bond would repress the tendency of the cycloheptyne to oligomerize sufficiently to make the isolation of 3,3,7,7-tetramethylcycloheptyne *(3)* possible.

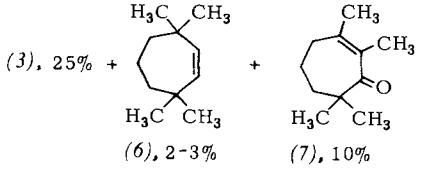


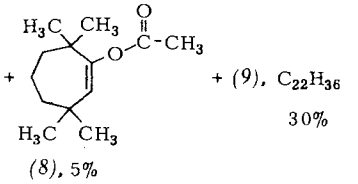
(1) *(2)* *(3)*



(4) *(5)*

We obtained *(3)* analogously to *(1)*, from 3,3,7,7-tetramethyl-1,2-cycloheptanedione *(4)*[4] by way of the bishydrazone *(5)* (yield 63%, m.p. 159—160°C) which was then oxidized by lead tetraacetate.





In this reaction there were formed, besides *(3)*, b.p. 25°C/0.01 torr, the compounds *(6)* to *(9)*, the last being a dimer of *(3)* of as yet unclarified structure.

The structure of *(3)* follows from spectroscopic data [mass spectrum, 150 (M^+); ^{1}H-NMR (60 MHz, CCl_4, referred to TMS), 1.54 ("s", 6 H), 1.13 ppm (s, 12 H); IR (CCl_4), 2190, 2170 cm^{-1} (νC≡C); Raman (no solvent), 2210, 2179, 2158 cm^{-1} (νC≡C)] and from oxidation to *(4)* by O_2.

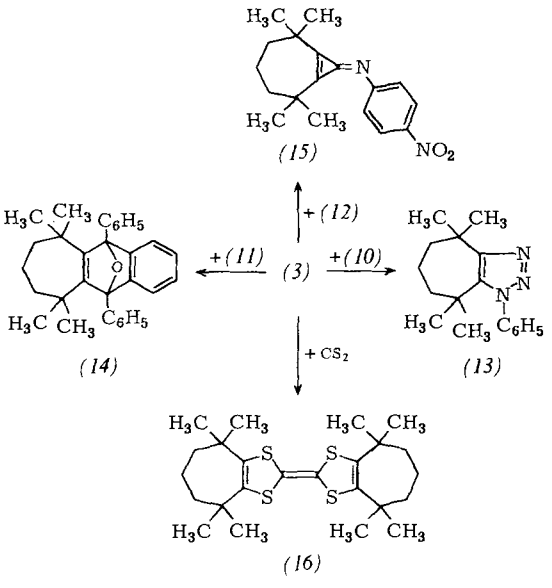
Compound *(3)* reacts rapidly at 25°C with phenyl azide *(10)*, 1,3-diphenylbenzo[*c*]furan *(11)*, and *p*-nitrophenyl isocyanide *(12)*, giving the corresponding 1:1 adducts *(13)*, m.p. 187—188°C, *(14)*, m.p. 165—166°C, and *(15)*, m.p. 143°C; with CS_2 under analogous conditions it affords the 2:2 adduct *(16)*, m.p. 330°C (dec.). The structures of these adducts are proved by spectroscopic data.

In contrast to *(1)*, *(3)* is unstable at 25°C: in 0.2 M CCl_4 solution its half-life amounts to about 1 day, but in the

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pure form it dimerizes within an hour to *(9)*, b.p. 125 °C/0.2 torr [mass spectrum, 300 (M^+); ^{1}H-NMR (60 MHz, CCl_4, referred to TMS), 5.60 (s, 1 H, =CH—), 4.67 (broad signal, 2 H, $=CH_2$), 2.2—1.0 (complex m, superimposed



on three s (each 6 H) at 1.20, 1.12, and 1.07 ppm, total 33 H, aliphatic H); IR (film), 3073 $=CH_2$, 1652 (C=C), 883 cm^{-1} ($=CH_2$); UV (C_6H_{12}), λ_{max} (ε) = 230 nm (11300)].

The addition of *(12)* permits a further comparison of the reactivities of *(1)* and *(3)*: compound *(3)* adds *(12)* about 20 times faster than does *(1)*[5].

These results show the following:

1. Substitution of the S ring member by a CH_2 group [*(1)* → *(3)*] causes a considerable increase in the reactivity of the seven-membered cycloalkyne.

2. Introduction of the four CH_3 groups [*(2)* → *(3)*] leads to a drastic increase in the kinetic stability of the cycloheptyne system; *(3)* dimerizes 10^7 to 10^8 times more slowly than *(2)*, which corresponds to an increase of 9—10 kcal mol^{-1} in the free enthalpy of activation for this reaction.

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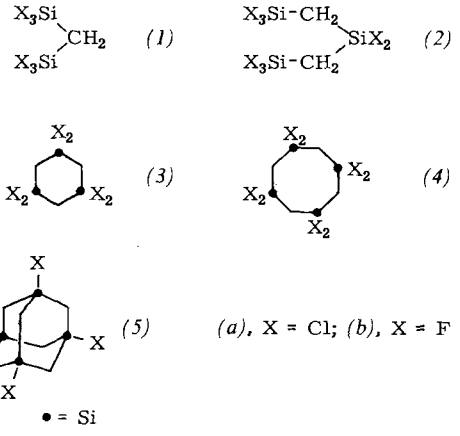
Si-Fluorinated Carbosilanes

By *Gerhard Fritz* and *Malte Berndt*[*]

In connection with our studies on perchlorinated "carbosilanes"[1-4] we now report the formation and properties of *Si*-fluorinated compounds of this type.

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The SiCl group in carbosilanes having an unsubstituted CH_2 bridge can be converted into a SiF group by treatment with ZnF_2. Compounds *(1b)*—*(5b)* are thus formed without skeletal cleavage from *(1a)*—*(5a)*.

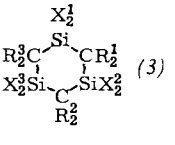


(a), X = Cl; *(b)*, X = F

(1a) and *(2a)* react with ZnF_2 at 20 °C in hexachlorobutadiene to give *(1b)*[5] (80% yield) and *(2b)*, respectively. In an analogous reaction in acetonitrile at 80 °C *(3a)* and *(4a)* afford *(3b)*[6] (m.p. 143 °C; sublimes at 75 °C/10^{-3} torr) and *(4b)* (m.p. 75 °C; sublimes at 60 °C/10^{-3} torr). Heating of a mixture of *(5a)* and ZnF_2 to 100—160 °C furnishes *(5b)* (m.p. 260 °C; sublimes at 60—70 °C/10^{-3} torr); above 200 °C, however, compound *(5a)* undergoes ring cleavage. The compounds containing the Si—F group are less sensitive to hydrolysis than those containing Si—Cl.

Reaction of the perchlorinated compounds $(Cl_3Si)_2CCl_2$ *(1c)* and $(Cl_3Si—CCl_2)_2SiCl_2$ *(2c)* with ZnF_2 at 20 °C in hexachlorobutadiene leads to $(F_3Si)_2CCl_2$ *(1d)*[5] (yield ≈95%) and $(F_3Si—CCl_2)_2SiF_2$ *(2d)*, respectively. Some degree of decomposition occurs during formation of *(2d)* and at 100 °C the decomposition reactions predominate to form SiF_4, F_3SiCCl_2H, and $(F_3Si)_2CCl_2$.

By contrast, no chlorine/fluorine exchange takes place at the silicon atoms of perchlorinated cyclic carbosilanes with ZnF_2 or $SbF_3/SbCl_5$. $(Cl_2Si—CCl_2)_3$ *(3c)* and $[(SiCl)_4(CCl_2)_6]$ *(5c)* undergo no reaction, for example, with ZnF_2 at room temperature, and at higher temperatures (80—150 °C) react only with ring cleavage. The completely *Si*-fluorinated derivatives also resist attempted preparation by reaction of ZnF_2 with the SiH groups of the corresponding *C*-chlorinated carbosilanes. Thus while $(C_2H_5)_3SiH$ readily gives $(C_2H_5)_3SiF$ on treatment with PF_5, $(H_3Si—CCl_2)_2SiH_2$ *(2e)* does not react with ZnF_2.



(3)

	X^1	X^2	X^3	R^1	R^2	R^3	M.p. (°C)	Subl. (°C/10^{-3} torr)
(3d)	F	F	F	Cl	Cl	Cl	64	40–60
(3e)	F	F	F	H	Cl	H	43	40
(3f)	F	F	F	Cl	Cl	H	—	—
(3g)	Cl	Cl	Cl	H	Cl	H	—[2, 4]	—[2, 4]
(3h)	F	F	F	H	Br	H	66	50
(3i)	Cl	Cl	Cl	H	Br	H	—[7]	—[7]
$(F_2Si—CCl_2)_4$ *(4c)*							75	60
$[(FSi)_4(CCl_2)_6]$ *(5d)*							240	180

Si-Fluorinated, *C*-chlorinated carbosilanes such as *(3d)*, *(4c)*, and *(5d)* are readily accessible in good yields, however, by photochlorination of the CH_2 groups in compounds of type *(3b)*—*(5b)* (see Table). ^{1}H-NMR studies of the reaction course in CCl_4 solution show that partially chlorinated derivatives, *e.g. (3e)* and *(3f)*, can also be prepared in the same way. Compound *(3e)* may be obtained by fluorination of *(3g)*[2,4] with ZnF_2 at 80°C in acetonitrile or benzene, and *(3h)* likewise from *(3i)*[7].

Si-Fluorinated, *C*-chlorinated carbosilanes are rapidly hydrolyzed by atmospheric moisture and differ considerably in their chemistry from the corresponding perchlorinated compounds. Thus $(F_3Si)_2CCl_2$ *(1d)* reacts with $LiCH_3$ to give $[(CH_3)_3Si]_2CCl_2$, whereas in the case of $(Cl_3Si)_2CCl_2$ *(1c)* methylation starts at the C—Cl bond and initially yields $(Cl_3Si)_2C(CH_3)Cl$[3].

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Molecular Perchlorato Complexes of Iridium(I), Rhodium(I), and Cobalt(I)[**]

By *J. Peone, Jr.* and *L. Vaska*[*]

We report the synthesis and some properties of *trans*-perchloratocarbonylbis(triphenylphosphane)iridium(I) *(1)* and -rhodium(I) *(2)*, as well as perchloratodicarbonylbis-(triphenylphosphane)cobalt(I) *(3)*, apparently the first examples of M^I (d^8) perchlorato complexes of transition metals. These compounds are of interest not only because they contain a covalent metal-$OClO_3$ linkage, but also for their versatility as starting materials for a variety of new complexes [*e.g.*, eq. (3)][1].

Complexes *(1)* and *(2)* are prepared by treating a saturated solution of the corresponding chloro compound of iridium(I)[2] and rhodium(I), respectively, in benzene with silver perchlorate (molar ratio 1:1) under nitrogen at 25°C.

$$[MCl(CO)(Ph_3P)_2] + AgClO_4 \rightarrow [M(OClO_3)(CO)(Ph_3P)_2] + AgCl \quad (1)$$
(1), M = Ir
(2), M = Rh

The reaction mixture, protected from light, is stirred for 15 min; the resulting silver chloride is filtered from a yellow-orange solution which, on addition of hexane, produces crystals of the perchlorato complex. Yields ranging from 80 to 95% have been obtained[3]. The yellow crystals of *(1)* are sensitive to O_2 and must be stored under N_2 or *in vacuo*; those of *(2)* are stable in air. The complexes have been identified by elemental analyses, IR spectra, and conductivity measurements (see Table).

(1) and *(2)* resemble their well-known congeners, $[MA(CO)L_2]$ (A = univalent anionic ligand, L = monodentate neutral ligand; *e.g.*, $[IrCl(CO)(Ph_3P)_2]$)[2,4-7], in most of their physical characteristics, but their chemical behavior is considerably more versatile [eq. (2), (3)][1,7]. The complexes *(1)* and *(2)* are insoluble in water and hexane, but soluble in polar organic solvents in which they undergo complete ionization

$$[M(OClO_3)(CO)(Ph_3P)_2] + S \rightarrow [M(S)(CO)(Ph_3P)_2]^+ + ClO_4^- \quad (2)$$
S = acetone, nitromethane, methanol, *etc.*

as evidenced by the conductivity data (Λ_M, Table).

Addition of Ph_3P to a C_6H_6 solution of *(1)* or *(2)* produces an orange [M = Ir, *(4)*] or yellow [M = Rh, *(5)*] precipitate of carbonyl*tris*(triphenylphosphane)metal(I) perchlorate.

$$[M(OClO_3)(CO)(Ph_3P)_2] + Ph_3P \rightarrow [M(CO)(Ph_3P)_3]ClO_4 \quad (3)$$
(1), M = Ir — *(4)*, M = Ir
(2), M = Rh — *(5)*, M = Rh

According to their elemental analyses, solubility characteristics (insoluble in nonpolar, soluble in polar solvents) and the properties summarized in the Table, *(4)* and *(5)* represent tetragonal cationic d^8 complexes analogous to those reported previously[8].

Table. Properties of complexes *(1)* to *(5)*.

	Complex [a]	Λ_M(ohm^{-1}) in CH_3OH [b]	IR in $CHCl_3$ (cm^{-1}) ν_{CO} [c]	IR in nujol (cm^{-1}), $OClO_3(C_{3v})$ and ClO_4 (T_d) absorptions [d]				
(1)	$[Ir(OClO_3)(CO)L_2]$	110	1990	1160(m)	1130(s)	1050(ms)	920(w)	620(ms)
(2)	$[Rh(OClO_3)(CO)L_2]$	100	2000	1160(m)	1130(s)	1070(ms)	920(w)	620(ms)
(3)	$[Co(OClO_3)(CO)_2L_2]$		1950, 2000	1160(m)	1125(s)	1080(ms)	928(mw)	623(ms)
(4)	$[Ir(CO)L_3]ClO_4$	120	2020		1100 (vs, br) [e]			620(ms)
(5)	$[Rh(CO)L_3]ClO_4$	105	2030		1100 (vs, br) [e]			620(ms)

[a] L = $(C_6H_5)_3P$. [b] 10^{-4}–10^{-5} M in complex. Molar conductance (Λ_M) of a standard 1:1 electrolyte, $[(C_3H_7)_4N]PF_6$, in CH_3OH is 110 ohm^{-1}. Acetone and nitromethane solutions of the complexes give similar results (essentially complete ionization). In chlorobenzene, Λ_M = 0.7 for *(1)* and 5.2 ohm^{-1} for *(4)*. [c] *(3)* measured in nujol. All bands very strong (vs). For comparison, $\nu_{CO}(CHCl_3)$ in $[IrCl(CO)L_2]$, 1967 cm^{-1}. [d] Full analysis of the spectra and assignments of the bands are given in ref. [7], see also ref. [9]. [e] Broad band centered at 1100 cm^{-1} and overlapping with a $(C_6H_5)_3P$ band near the same frequency.

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The principal evidence for the coordinated perchlorato group ($OClO_3$) in the crystals of *(1)*, *(2)*, and *(3)* derives

from the infrared data given in the Table. According to previous analyses of the spectra of related complexes[9], these compounds contain $OClO_3$ of C_{3v} symmetry, and *(4)* and *(5)* an uncomplexed $ClO_4(T_d)$ unit. The molecular structures of *(1)* and *(2)* must prevail also in nonpolar solvents as suggested by their electronic spectra in benzene, which are identical with those of the respective complexes in the solid state as well as very similar to the spectra (solution and crystals) of the structurally well-established *trans*-$[MA(CO)L_2]$[7]. Note also the striking solubility difference in benzene between the ionic complexes [*(4)* and *(5)*, insoluble] and the neutral species [*(1)* and *(2)*, soluble]. The latter, by analogy with *trans*-$[MA(CO)L_2]$[4], undergo oxidative addition reactions to produce six-coordinated molecular complexes of tervalent metals[1,7].

Perchloratodicarbonyltris(triphenylphosphane)cobalt(I) *(3)*, a five-coordinated complex, is obtained from a benzene solution of the reactants and precipitated with hexane.

$$[CoCl(CO)_2(Ph_3P)_2] + AgClO_4 \rightarrow [Co(OClO_3)(CO)_2(Ph_3P)_2] + AgCl \quad (4)$$

It appears that the method of synthesis for *(1)*, *(2)*, and *(3)* represents a general route to organometallic perchlorato compounds[10].

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[10] Although we have thus far experienced no accidents in our work with these complexes, it should be mentioned that crystalline *trans*-$[Ir(OClO_3)(CO)(Ph_3P)_2]$ reacts violently with chlorine gas. Needless to add that all these materials are potentially hazardous and one should employ only small amounts, avoid high temperatures and provide adequate shielding and other protective measures. See *M. Burton*, Chem. and Eng. News *28*, No. 53, p. 55 (1970).

Crystal and Molecular Structure of Tricarbonyl(hexaethylborazine)chromium(0)[**]

By *Gottfried Huttner* and *Bernhard Krieg*[*]

It is to be expected that investigation of the structure of π-complexes of transition metals with heterocyclic π-ligands will give an insight into the bonding in π-complexes, particularly on comparison with analogous complexes of carbocyclic systems. Replacing a carbon atom by a hetero atom amounts, in a first approximation, to a change in the electron density distribution in the ligands, and the influence of such changes can be studied in structural investigations.

The first structure determination that we report in this connection is the X-ray analysis of tricarbonyl(hexaethylborazine)chromium(0), a compound that is isosteric with tricarbonyl(hexaethylbenzene)chromium(0). Because of its bulky ethyl groups, the complex is not the ideal representative of the borazine-metal π-complexes, but it was selected for investigation because it is the only borazine complex prepared so far that has been obtained in usable single crystals[7].

The compound, $[(C_2H_5)_6B_3N_3]Cr(CO)_3$, crystallizes in the monoclinic space group $P2_1/c$, with $a = 12.05$, $b = 17.88$, $c = 14.79$ Å, $\beta = 138.6°$, $d_{calc} = 1.214$, $d_{exp} = 1.218\,g\,cm^{-3}$, $Z = 4$. The crystal used for the structure determination measured $0.2 \times 0.3 \times 0.4$ mm. For this, a total of 918 independent reflection intensities were measured on a two-circle diffractometer with $Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å. The structure was solved by the heavy atom method and refined to an *R* factor of 0.070 by successive approximations; all the hydrogen atoms were located. The geometry of the molecular skeleton (Fig. 1) corresponds to that of tricarbonylbenzenechromium, as predicted by *Werner et al.*[1]. However, the structure shows some peculiarities.

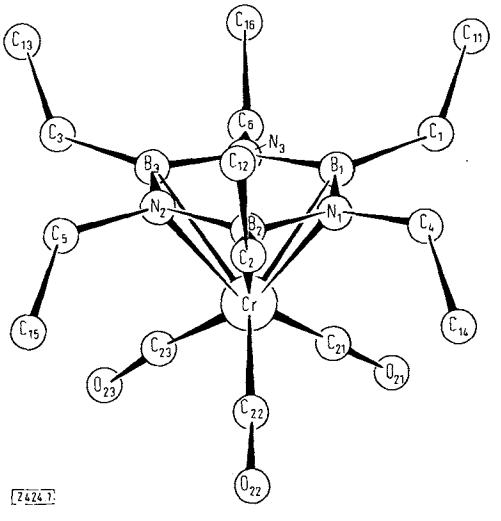


Fig. 1. Molecular structure of tricarbonyl(hexaethylborazine)chromium(0).

The idealized three-fold axis of the tricarbonylchromium group is perpendicular to the borazine ring. The nitrogen atoms of the ring are staggered with respect to the carbonyl groups, and the N—Cr bonds are directed toward the Cr—(CO) bonds. As in the tricarbonylchromium derivatives of 1-methylpyrrole and 1,4-dimethyl-1,2-dihydropyridine, the nitrogen, as the ring atom with the highest electron density, is *trans* to a carbonyl group[2]. The mean Cr—N distance amounts to 2.22 Å; this is considerably shorter than the Cr—B distances (mean 2.31 Å, Table 1); the difference between these bond lengths corresponds approximately to the difference between the covalent radii of boron and nitrogen[3] and it is thus not permissible to conclude that the boron atoms are bonded more weakly to the metal than the nitrogen atoms.

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The differing Cr—B and Cr—N bond lengths lead to puckering of the borazine skeleton. In contrast to the situation in free hexaethylborazine, which is planar within experimental error[4], the two parallel planes formed by the three boron atoms and the three nitrogen atoms are separated by 0.07 Å. The six-membered ring thus assumes a not very pronounced chair conformation (see the torsion angles in Table 1), which has an effect on the positions of the ethyl groups. Whereas in free hexaethylborazine[4] the ethyl groups project alternately above and

Table 1. Bond lengths, bond angles, and torsion angles in tricarbonyl(hexaethylborazine)chromium(0).

Bond lengths (Å)

Cr—B(1)	2.30±0.02	Cr—N(1)	2.23±0.01
Cr—B(2)	2.33±0.02	Cr—N(2)	2.24±0.01
Cr—B(3)	2.31±0.02	Cr—N(3)	2.18±0.01
B(1)—N(1)	1.46±0.02	N(1)—B(2)	1.36±0.02
B(2)—N(2)	1.45±0.02	N(2)—B(3)	1.44±0.02
B(3)—N(3)	1.47±0.02	N(3)—B(1)	1.46±0.02

Bond angles (degrees)

N(1)—B(1)—N(3)	113±1	B(1)—N(1)—B(2)	127±2
N(2)—B(2)—N(1)	116±1	B(2)—N(2)—B(3)	123±2
N(3)—B(3)—N(2)	115±1	B(3)—N(3)—B(1)	123±1

Torsion angles (degrees)

B(1)—N(1)—B(2)—N(2)	6	N(1)—B(2)—N(2)—B(3)	− 8
B(2)—N(2)—B(3)—N(3)	12	N(2)—B(3)—N(3)—B(1)	− 14
B(3)—N(3)—B(1)—N(1)	12	N(3)—B(1)—N(1)—B(2)	− 8
B(1)—N(1)—B(2)—C(2)	−169	N(1)—B(2)—N(2)—C(5)	179
B(2)—N(2)—B(3)—C(3)	−169	N(2)—B(3)—N(3)—C(6)	168
B(3)—N(3)—B(1)—C(1)	−161	N(3)—B(1)—N(1)—C(4)	177

below the plane of the ring, in the complex the ethyl group C(6)—C(16) breaks this alternation. This is possible because the ring puckering increases the distance between the methylene carbon atoms C(6) and C(3), and C(6) and C(1), so that there is no longer strong steric hindrance between their hydrogen atoms.

As in free borazine[5], the bond angles N—B—N (mean value 115°) are smaller than the B—N—B angles (mean 124°). The mean of the B—N separations (1.44 Å) does not differ from that (1.435±0.002 Å) in the free borazine[5]. However, one of the B—N distances (Table 1), at 1.36 Å, deviates appreciably from the mean value; a similar strong deviation was found[6] for the ring distances within a π-bonded ring in the case of tricarbonyl(hexamethylbenzene)chromium(0), where the C—C distances differ by up to 9/100 Å; in neither case is there any immediately obvious explanation of these observations. The Cr—$C_{(CO)}$ distances, at 1.80 Å, are, within experimental error, the same as in tricarbonyl(hexamethylbenzene)chromium(0) (1.80 Å) and indicate a similar donor/acceptor behavior of benzene and borazine.

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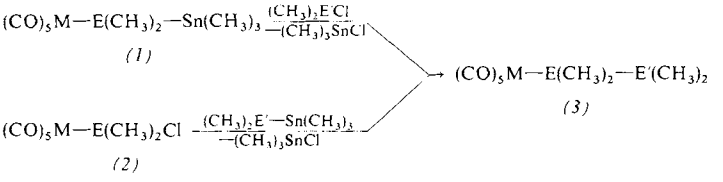
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Stepwise Formation of Bridged Dinuclear Carbonylmetal Complexes[1]

By *Heinrich Vahrenkamp* and *Winfried Ehrl*[*]

Very few reports have hitherto appeared concerning metal carbonyls in which two metal atoms are held together only by an atom that behaves as a Lewis base; their synthesis, *e.g.* that of $(CO)_5W—P(CH_3)_2—Re(CO)_5$[2] gives rise to difficulties. In contrast, dinuclear complexes exhibiting considerable stability, such as $(CO)_4Fe—P(CH_3)_2—P(CH_3)_2—Fe(CO)_4$[3], in which the carbonylmetal groups are linked *via* diphosphanes or diarsanes, have been known for some time. All known complexes of this kind are symmetrical, *i.e.* two identical bridging atoms link two identical metal atoms.

We have now accomplished the stepwise formation of such complexes having two-membered bridges in which the two metal atoms are different and the two bridge atoms are also different. We started with derivatives of hexacarbonylchromium and hexacarbonyltungsten with dimethylphosphido and dimethylarsenido ligands. The reactive complexes $(CO)_5M—E(CH_3)_2—Sn(CH_3)_3$ *(1)*, which are readily accessible photochemically, react with the halides $(CH_3)_2E'Cl$ to give the organometallic Lewis bases $(CO)_5M—E(CH_3)_2—E'(CH_3)_2$ *(3)*. Reaction of the complexes $(CO)_5M—E(CH_3)_2Cl$ *(2)* with the tin compounds $(CH_3)_2E'—Sn(CH_3)_3$ likewise leads to *(3)*. Photochemical reaction of compounds *(3)* with a hexacarbonylmetal affords the dinuclear complexes *(4)* in good yield.



$$(3) + (CO)_5M'(OC_4H_8) \xrightarrow{-OC_4H_8} (CO)_5M—E(CH_3)_2—E'(CH_3)_2—M'(CO)_5 \quad (4)$$

M, M′ = Cr, W; E, E′ = P, As

Each one of the ten conceivable complexes *(4)* with M = Cr or W and E = P or As has been prepared (see Table). *(4a)–(4c)* have already been described[4]. According to this method, *(4e)–(4j)* can be prepared by two analogous routes depending on the reactants.

Table. Properties of compounds *(4)*.

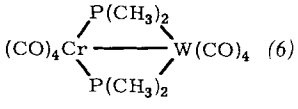
	M	E	E′	M′	M.p. (°C)	^{1}H-NMR [a] δ(E—CH_3)	J(P—H)	δ(E′—CH_3)	J(P—H)
(4a)	Cr	P	P	Cr	128	−1.04		−1.04	
(4b)	W	P	P	W	164	−1.14		−1.14	
(4c)	Cr	As	As	Cr	112	−1.05		−1.05	
(4d)	W	As	As	W	143	−1.14		−1.14	
(4e)	Cr	P	P	W	145	−1.00	6.2; 10.6	−1.22	6.2; 9.8
(4f)	Cr	As	As	W	125	−0.98		−1.18	
(4g)	Cr	P	As	Cr	114	−1.05	6.3	−1.00	7.8
(4h)	W	P	As	W	147	−1.17	6.0	−1.08	8.2
(4i)	Cr	P	As	W	126	−0.98	6.1	−1.14	8.0
(4j)	Cr	As	P	W	131	−0.95	8.2	−1.23	6.3

[a] Recorded in benzene; chemical shifts in ppm (TMS internal standard); coupling constants in Hz.

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The complexes are stable in air; their color ranges from intense yellow in the case of *(4c)* to colorless in the case of *(4b)*, thus paralelling the decrease in arsenic and chromium content. The IR spectra in the CO stretching region of all compounds *(4)* are almost identical and consist of a weak band at about 2065 cm^{-1} and a very strong (sometimes split) band at about 1945 cm^{-1}. The most important analytical information is provided by the ^{1}H-NMR spectrum (see Table) whose assignment is confirmed by measurements at 60 and 100 MHz. All the spectra show the expected number of singlets or doublets and, in particular, permit a distinction to be made between the otherwise highly similar isomers *(4i)* and *(4j)*. In this, as in other cases[5], P—H coupling is stronger over three bonds (8–10 Hz) than over two bonds (6 Hz).

Two extensions of the above reaction scheme come to mind. On the one hand there is the possibility of introducing other metal atoms. Thus $(CO)_5Cr—P(CH_3)_2—P(CH_3)_2$ and $Fe_2(CO)_9$ give a good yield of the yellow, readily soluble compound $(CO)_5Cr—P(CH_3)_2—P(CH_3)_2—Fe(CO)_4$ *(5)*, m. p. 96 °C. However, more important is the use of complexes *(4)* for the synthesis of strongly associated metal-carbonyl clusters. Thus thermolysis[6] of *(4e)* at 250 °C in benzene smoothly yields the new red complex $(CO)_4Cr[P_2(CH_3)_4]W(CO)_4$, dec. pt. 326 °C, whose diamagnetism and IR and NMR spectra indicate structure *(6)* with a chromium-tungsten bond.



(6)

It may be assumed that systematic exploitation of the above reactions will open up a new route to polynuclear transition metal complex systems and thus into the region between molecular compounds and the pure metals.

Procedure:

$(CO)_5W—As(CH_3)_2—Sn(CH_3)_3$ (1 mmol) and $(CH_3)_2PCl$ (1.1 mmol) in benzene (10 ml) are stirred for 2h with exclusion of air. All volatile components are subsequently removed in a high vacuum, leaving $(CO)_5W—As(CH_3)_2—P(CH_3)_2$ as a yellow oil. To this oil is added a solution of $(CO)_5Cr(OC_4H_8)$ (1.2 mmol) produced photochemically[7]. The reaction mixture is evaporated to dryness and the excess of $Cr(CO)_6$ is pumped off. After extraction with warm light petroleum (50 ml) and filtration the filtrate is also evaporated to dryness and the residue is recrystallized from cyclohexane (5 ml). The yield of pale yellow, air-stable *(4i)* is 0.38 g (55%).

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Redox Behavior of Insoluble Quinone/Hydroquinones

By *Hartmut Alt, Horst Binder, Alfons Köhling*, and *Gerd Sandstede*[*]

Solutions of quinones and hydroquinones have long been known as reversible redox systems, and the mechanism of oxidation and reduction has been repeatedly investigated. It has been shown that the electrode kinetics of duroquinone in aqueous-methanolic solution corresponds to that of *p*-benzoquinone[1]. We have studied the electrochemical properties (redox potential, reversibility of the reaction, and discharge characteristics) of insoluble quinones as solid electrodes because we were considering quinones as cathode material for secondary cells and fuel cells; the known nitro compounds are suitable only for primary cells as they are reduced irreversibly[2].

We have prepared conducting electrodes from non-conducting quinones by mixing them with graphite in weight ratio 1:1 and compressing the powder mixture between graphite felt disks. In some experiments the electrodes contained the quinones in a gold skeleton. The measurements were carried out with tetrachloro-*p*-benzoquinone (chloranil), tetramethyl-*p*-benzoquinone (duroquinone), and diphenoquinone, which are almost insoluble in aqueous electrolytes. The redox behavior was investigated by cyclic voltammetry using a triangular sweep with slow alteration of voltage[3,4]. The electrode potential[5] is increased linearly with time and after having reached a preselected value continuously reduced. The electrode then responds with an anodic current (oxidation of the hydroquinone to quinone) or—on lowering of the voltage—with a cathodic current (reduction of the quinone to hydroquinone). The cyclic potentiodynamic current-voltage curve obtained in this way for a chloranil electrode in 2 N H_2SO_4 (Fig. 1) is symmetrical with respect to the rest potential. The latter amounts to

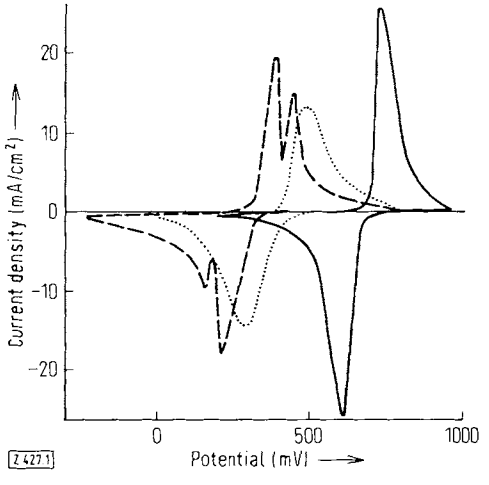


Fig. 1. Cyclic potentiodynamic current-voltage curves of a chloranil electrode. 9 mg of chloranil mixed with graphite in a gold support. Electrode surface, 1 cm^2; alteration of voltage, 40 mV/min. —— 3 N H_2SO_4; - - - - 5 M NH_4Cl; · · · · 2 M $ZnCl_2$.

668 mV and is obtained when quinone and hydroquinone exist simultaneously in the electrode. A redox potential of 664 mV was measured in aqueous-alcoholic solution[6]. The cyclic current-voltage curve (Fig. 1) has a very narrow

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oxidation maximum and a similar reduction maximum; the charge and discharge polarization is very small. Further, the areas are identical and correspond to the amount of charge contained in the substance. Hence, quinone can be used in the present solid form completely reversibly to the extent of 100%. The cyclic current-voltage curve is stationary; the capacity and the resistance of the electrode change, if at all, only after a long time.

The cyclic current-voltage curve measured in zinc chloride solution shows the same behavior (Fig. 1). The rest potential is *ca.* 400 mV, corresponding to a pH of 4.8. However, in ammonium chloride solution (pH ≈ 4.5) the rest potential is *ca.* 100 mV less than the redox potential calculated on the basis of the theoretical pH-dependence. Further, the current maxima of the cyclic potentiodynamic current-voltage curves are split (Fig. 1); on charge and discharge two maxima are obtained that are separated by *ca.* 70 mV; these maxima are assigned to the two electron transfer reactions quinone/semiquinone and semiquinone/hydroquinone—since chloranil does not form a quinhydrone[6], it must be assumed that the intermediate product is the semiquinone which is stabilized by the ammonium ions and reacts further only at higher (or lower) potential. The discharge curves, measured galvanostatically in dilute sulfuric acid, are almost horizontal at medium current density, at least up to 90% discharge, and the polarization on discharge amounts to only 20 to 60 mV with respect to the rest potential (Fig. 2). Further it can be seen from the

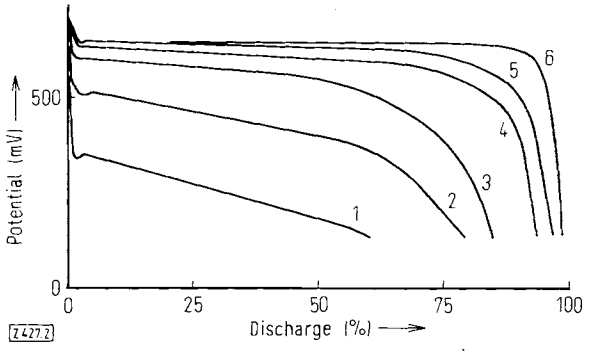


Fig. 2. Discharge curves of a chloranil cathode. 184 mg of chloranil mixed with graphite. Electrode surface, 1 cm²; 3 N H_2SO_4; 25 °C. Curve 1: 600 mA/cm² = 10 C [7]. Curve 2: 300 mA/cm² = 5 C. Curve 3: 120 mA/cm² = 2 C. Curve 4: 60 mA/cm² = 1 C. Curve 5: 30 mA/cm² = 0.5 C. Curve 6: 3 mA/cm² = 0.05 C.

Figure that the quinone cathode can be particularly heavily loaded. It is true that the practical capacity decreases with increasing current density, but it still amounts to 85% of the theoretical value at a discharge rate of 2 C[7]. Even a load of 600 mA/cm² does not lead to voltage breakdown. The chloranil cathode, further, can be heavily loaded even at low temperature; at 0 °C polarization is only *ca.* 50 mV larger than at room temperature. Also, the discharge characteristics in the salt solutions mentioned are almost horizontal. Therefore, it would also be possible to use quinone cathodes in primary cells having greater load capacity for neutral electrolytes, for which purpose zinc might, for example, be introduced as anode material. Again, development of secondary cells would be of interest, because higher energy densities (Wh/kg) can be obtained than with lead accumulators. Our experiments with a chloranil electrode in aprotic solvents have shown that this electrode behaves reversibly also in organic electrolytes, *e.g.*, lithium perchlorate in acetonitrile or propylene carbonate, and this makes it possible to develop a high-energy battery with lithium anodes.

Quinone cathodes in aqueous electrolytes can be regenerated by air. Normally hydroquinones are not oxidized by oxygen, but the capacity of chloranil or duroquinone in contact with catalytically active charcoal was regenerated quantitatively after discharge in dilute sulfuric acid or ammonium chloride solution provided that air is supplied by use of a hydrophobic electrode[8]. Since the active mass was hydrophilic, oxidation of the hydroquinone occurs by an electrochemical mechanism. At the redox potential of the quinone the oxygen is cathodically reduced and the hydroquinone anodically oxidized simultaneously at the same electrode. Regeneration can also be achieved by hydrogen peroxide.

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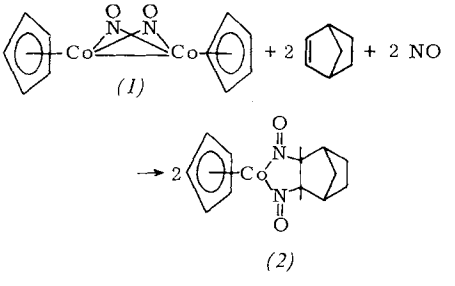
[7] A discharge rate of 1 C denotes that discharge is at a current strength such that the total charge capacity (in Ah) of the electrode is consumed in 1 h. The quantity thus has the dimensions [total amount of charge/h]; a discharge rate of 2 C corresponds to discharge at double the current strength, *i.e.* to a discharge time of 0.5 h.

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Incorporation of Olefin and Nitric Oxide into Organocobalt Compounds[**][1]

By *Henri Brunner* and *Stephan Loskot*[*]

The system consisting of olefin, CO, and organocobalt compound is of considerable technical importance, particularly for carbonylations[2]. We have studied the system consisting of olefin, NO, and organocobalt compound and report here a synthesis starting from these three components.



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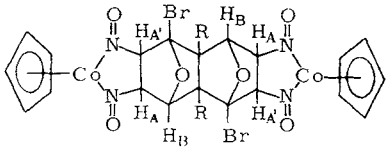
[**] This work was supported by the Deutsche Forschungsgemeinschaft.

$C_5H_5Co(CO)_2$ reacts with NO to give $[C_5H_5Co(NO)]_2$ *(1)*[3]. However, in the presence of norbornene the new complex *(2)* is formed. The latter can also be obtained from *(1)*, norbornene, and NO at room temperature and atmospheric pressure in 90% yield.

Compound *(2)* forms dark crystals, stable in air and soluble with an intense red color in organic solvents except aliphatic hydrocarbons; it is monomeric in benzene. In its mass spectrum the molecular ion appears at $m/e = 278$; fragmentation of the molecule (removal of the olefin, followed by stepwise loss of the NO groups) indicates coordination of the ligands through the NO groups to the cobalt atom. The IR spectrum of *(2)* in KBr does not contain any band in the region of NO ligands bound terminally to metal[4]; an intense band at 1357 cm^{-1} can be ascribed to the NO stretching vibration weakened by back donation.

The signal for olefinic protons in the ^{1}H-NMR spectrum of norbornene lies at $\tau = 4.02$[5]. The corresponding protons of *(2)* give rise to a doublet at $\tau = 7.28$ with a coupling constant of about 1 Hz. The signal for the bridgehead protons is shifted from $\tau = 7.16$ to $\tau = 7.36$ by complex formation. The signal for the π-bonded C_5H_5 ring appears at $\tau = 5.04$.

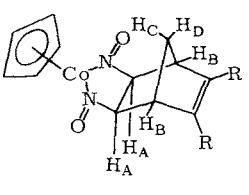
In order to elucidate the structure of the new type of compound, derivatives were used containing substituted cyclic olefins instead of norbornene. The double Diels-Alder adduct from 2-bromofuran and dimethyl acetylenedicarboxylate yields the complex *(3)* in which both olefinic double bonds have reacted.



(3), R = $COOCH_3$

In the ^{1}H-NMR spectrum of *(3)* the protons H_A and $H_{A'}$ give rise to an AB system with resonances at $\tau = 6.43$ and $\tau = 6.80$ and a coupling constant of 5.7 Hz. These two protons thus occur in the "nitroso" structure *(3)* on neighboring carbon atoms. The "oxime" structure, which would be formed by shift of the protons H_A and $H_{A'}$ on to the oxygen atoms is thus excluded. The signal for the bridgehead proton H_B lies at $\tau = 4.49$. H_B does not couple with H_A and $H_{A'}$.

When the Diels-Alder adduct from cyclopentadiene and dimethyl acetylenedicarboxylate reacts with $[C_5H_5Co(NO)]_2$ and NO, only the unsubstituted double bond reacts, with formation of *(4)*. The ^{1}H-NMR spectrum of *(4)* contains a doublet for H_A at $\tau = 6.77$ and a multiplet



(4), R = $COOCH_3$

for H_B at $\tau = 6.54$. H_C and H_D form an AB system (H_C at $\tau = 7.84$; H_D at $\tau = 8.20$) with a coupling constant of 10 Hz. Each line of the AB system shows additional fine structure. The chemical shifts and coupling constants of the hydrogen atoms H_A to H_D were assigned by double resonance. As was previously noted for *(3)*, H_A and H_B do not couple with one another in *(4)*. The constant of the long-range coupling $H_A - H_D$ amounts to 1.3 Hz.

The long-range coupling between H_A and H_D in *(4)* as well as the absence of coupling of H_A and H_B in *(3)* and *(4)* are considered as characteristic of *endo*-protons H_A in systems of the type *(3)* and *(4)*[6]. The *exo*-structure is thus to be ascribed to the complexes *(3)* and *(4)*.

Similar complexes are formed from ethylene and cyclohexene but have not yet been obtained pure.

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Phenylarsenic(v) Trichloride Azide and Phenylarsenic(v) Chloride Nitride[1]

By *Volker Krieg* and *Johann Weidlein*[*]

Phenylarsenic dichloride dissolved in CCl_4 reacts with gaseous chlorine azide[2] exothermally according to

$$C_6H_5AsCl_2 + ClN_3 \rightarrow C_6H_5AsCl_3N_3 \quad (1)$$

Removal of solvent and unreacted starting materials under reduced pressure leaves highly viscous, orange-red phenylarsenic(v) trichloride azide *(1)*. The compound is only moderately soluble in benzene and is hydrolyzed by water with evolution of considerable amounts of heat. On rapid heating it decomposes, with black coloration, but not explosively. Compound *(1)* is, however, also unstable at room temperature and slowly gives off chlorine and nitrogen; thermal decomposition proceeds according to

$$C_6H_5AsCl_3N_3 \rightarrow C_6H_5AsClN + Cl_2 + N_2 \quad (2)$$

and goes to completion only at about 100 °C in a high vacuum; phenylarsenic(v) chloride nitride *(2)* is evolved. Compound *(2)* is a slightly brownish glass at room temperature whose softening point lies at about 70 °C. The hygroscopic compound dissolves in organic solvents and in weak alkalis. Cryoscopic molecular weight determinations in benzene show the substance to exist as the trimer.

In the IR spectrum of *(1)* the characteristic absorption bands of the azido group can be assigned unequivocally.

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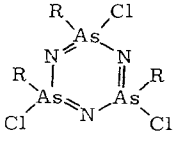
They occur at 2055 ($\nu_{as}N_3$), 1240 (ν_sN_3), 470 cm^{-1} (δN_3). Further deformational vibrations of the azido group are probably masked by the strong bands at 670 (r) and 740 cm^{-1} (γC—H). The "X-sensitive" vibrations q, r, t, and y[3] of the C_6H_5As group are shifted by only about 10 cm^{-1} towards longer wavelengths compared to $C_6H_5AsCl_2$[4]. However, a very strong and poorly structured band between 960–1020 cm^{-1}, which is absent from the spectrum of $C_6H_5AsCl_2$, is particularly noticeable. Although the phenyl ring vibration will be present at 1000 cm^{-1}, the main contribution certainly comes from As—N stretching vibrations. The frequency can only be explained in terms of extensive As—N π bonding, as in the arsenic nitride compounds $[(C_6H_5)_2AsN]_4$[5] and $[C_6H_5AsClN]_3$ *(2)* where association gives rise to an alternating sequence of As—N single and double bonds. The α-N atom of the azo group can admittedly function as donor atom owing to its lone pair, as in the organometal azides of Group IIIB elements[2,6]; however, in *(1)* the negative inductive effect of the three chlorine atoms and the phenyl group should rather promote an interaction of the lone pair with an empty d orbital of arsenic. In this way a (p→d)π bond is superimposed on the As—N σ bond.

Table. Characteristic IR frequencies of compounds *(1)* and *(2)*.

Vibration	$[C_6H_5AsCl_3N_3]$ [a]	$[C_6H_5AsClN]_3$ [a]
$\nu_{as}N_3$	2055 vs [b]	—
ν_sN_3	1240 m	—
q [c]	1070 s	1090 vs
νAs—N—As(+$\nu_sC_6H_5$)	970 vs (br)	945 vs 930 sh
r(+δAs—N—As) [c]	670 vs	640 vs
δN_3	470 s-m	468 vs
y [c]	450 vs	—
νAs—Cl	400 vs (br)	390 vs 375 sh
t [c]	290 vs (br)	330 vs

[a] Assignment based on vibrational spectrum of $C_6H_5AsCl_2$.
[b] Values given in cm^{-1}.
[c] Designation of "X-sensitive" vibrations (q, r, y, t) according to *Whiffen* [3].

By analogy with tetrameric diphenylarsenic nitride[5] a ring structure can be assumed for trimeric phenylarsenic(v) chloride nitride.



(2), R = C_6H_5

The six-membered ring system can have C_{3v}, C_s, or C_1 symmetry, depending upon the positions of the ligands Cl and R. It is not possible to distinguish between a planar and a puckered As_3N_3 ring on the basis of the IR spectrum alone.

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Dynamics of the Photodimerization of 9-Anthroic Acid and Sodium 9-Anthroate[1][**]

By *Dwaine O. Cowan* and *Walter W. Schmiegel*[*]

While many anthracene derivatives are known to photodimerize only the photodimerization of unsubstituted anthracene has been studied in mechanistic detail[2]. To learn more about the effect of solvent and substituents on radiative and nonradiative processes we have studied the photodimerization of 9-anthroic acid in ethanol and benzonitrile and the photodimerization of sodium 9-anthroate in water, deuterium oxide, and benzonitrile.

The material balance (dimer and starting compound) for the preparative photolysis of degassed solutions of the purified acid and sodium salt in each of the solvents was greater than 93% with only traces of nonacidic material. The non-acidic material was principally anthraquinone[3].

Process	Rate	
$A + h\nu \rightarrow A^s$	I_a	Light absorption
$A^s \rightarrow A + h\nu$	$k_F[A^s]$	Fluorescence
$A^s \rightarrow A$	$k_{IC}[A^s]$	Internal conversion
$A^s \rightarrow A^t$	$k_{ISC}[A^s]$	Intersystem crossing
$A^s + A \rightarrow 2A$	$k_{CQ}[A^s]\,[A]$	Concentration quenching
$A^s + A \rightarrow D$	$k_{DIM}[A^s]\,[A]$	Dimerization

Scheme 1.

To obtain meaningful assessments of the photochemical reactivity it is necessary to determine specific rate constants. Quantum yield measurements represent rate ratios and are therefore insufficient to indicate specific reactivities. To obtain the specific rate constants and verify the mechanism suggested in Scheme 1 the following was carried out: *first*, the fluorescence lifetimes in dilute solutions (τ_F^0) were measured by the phase shift method[4]; *second*, the absolute fluorescence quantum yields in dilute solutions (Φ_F^0) were determined by comparison with the fluorescence quantum yield of quinine sulfate after the spectra had been corrected for phototube wavelength response; *third*, relative quantum yields of fluorescence as a function of concentration were measured over the concentration range at which the dimerization was studied[5]; and *fourth*, the low conversion quantum yield of dimer formation as a function of concentration was determined using the equipment previously described[6].

The mechanism given in Scheme 1 would predict the following relationships:

$$\Phi_F^0 = k_F/(k_F + k_{ISC} + k_{IC})$$

$$1/\Phi_F = (k_F + k_{ISC} + k_{IC})/k_F + \{(k_{DIM} + k_{CQ})\,k_F\} \cdot [A]$$

$$1/\Phi_{DIM} = (k_{DIM} + k_{CQ})/k_{DIM} + \{(k_F + k_{ISC} + k_{IC})/k_{DIM}\} \cdot \frac{1}{[A]}$$

This mechanism was found to be consistent with the observations that a plot of the reciprocal of the relative quantum yield of fluorescence $1/\Phi_F$ *vs* the anthracene concentration [A] yields a straight line and a plot of the reciprocal of the quantum yield of dimerization $1/\Phi_{DIM}$ *vs* the reciprocal of the anthracene concentration 1/[A] gives a straight

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[***] Guggenheim Fellow. On leave from the Johns Hopkins University.

line. Since the intercept of $1/\Phi_{DIM}$ *vs* $1/[A]$ is not unity the concentration quenching process (k_{CQ}) must be important. This may suggest an excimer intermediate but our kinetic data does not demand this intermediate.

$A^s + A \rightleftarrows [A...A]^s$ excimer
$[A...A]^s \rightarrow$ Dimer
$[A...A]^s \rightarrow 2A$

From the slope and intercept of the dimerization graphs and the values of τ_F^0 and Φ_F^0 it is possible to calculate the rate constants given in Table 1. Only qualitative trends in rate constants will be considered in this communication.

All of the values for k_F are similar except for the sodium salt in benzonitrile. For this system the sum of the second order rate constants ($k_{CQ}+k_{DIM}$) exceeds the diffusion controlled collision rate constant (k_{DIFFN}). This may reflect an aggregation phenomenon resulting from ion-pairing. The small rate constant for dimerization and abnormally large concentration quenching rate constant may then be a result of an unfavorable dimerization geometry in the ion pair. The similar values of k_{DIM} of the 9-anthroic acid ion in water, deuterium oxide and the acid in acidic ethanol indicate that coulombic repulsion between the anions is not as large as expected.

The large Stokes shift observed between the absorption and fluorescence spectra of the acid (40 nm in benzonitrile, 50 nm in ethanol) compared to the small Stokes shift of the anion (6—9 nm)[7] should place the lowest excited singlet state of the acid below the second triplet state. Since intersystem crossing is normally to the second triplet which is approximately isoenergetic with the first excited singlet state this lowering of the singlet state energy can nicely account for the lower rate constants found for intersystem crossing of the acid[8].

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Table 1. Specific rate constants for the photodynamics of 9-anthroic acid and sodium 9-anthroate at 25°C.

System [a]	Φ_F^0 $\times 10^2$	τ_F^0 (ns)	k_F $\times 10^{-7}$	$k_{ISC}+k_{IC}$ $\times 10^{-7}$	k_{DIM} $\times 10^{-7}$	k_{CQ} $\times 10^{-7}$	$k_{DIM}+k_{CQ}$ $\times 10^{-7}$	k_{DIFFN} $\times 10^{-7}$
9-COOH EtOH, $H^{\oplus}$	21.8	4.55	4.79	17.2	102	428	530	613
9-COOH PhCN	64.6	12.3	5.24	2.88	35.9	298	334	532
9-COONa PhCN	4.88	2.65	1.84	31.9	11.3	1440	1451	532
9-COONa H_2O	6.89	1.50	4.59	62.1	73.0	657	730	739
9-COONa D_2O	5.54	1.35	4.17	69.8	76.9	307	384	598

[a] First order rate constants (s^{-1}); second order rate constants ($mol^{-1}\,l\,s^{-1}$).

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[4] *J. B. Birks* and *I. H. Munro* in *G. Porter*: Progress in Reaction Kinetics, Vol. 4, Pergamon Press, New York, 1968. We wish to thank the Central Research Department of E. I. Du Pont de Nemours & Co. for generously allowing us to use their phase shift instrument.

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[6] *D. O. Cowan* and *A. A. Baum*, J. Amer. Chem. Soc. *93*, 1153 (1971).

[7] *T. C. Werner* and *D. M. Hercules*, J. Phys. Chem. *73*, 2005 (1969); *74*, 1030 (1970).

[8] Preliminary experiments indicate that k_{IC} is small in comparison with k_{ISC}, consequently the values of $k_{ISC}+k_{IC}$ in Table 1 can be regarded as values of k_{ISC}.

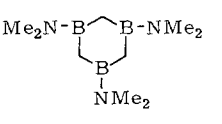
CONFERENCE REPORTS

Structural Problems in Boron-Nitrogen and Boron-Sulfur Chemistry

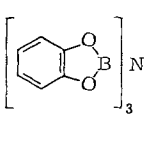
By *Heinz Hess*[*]

The past few years have seen various structural determinations, employing X-ray and electron diffraction techniques, on boron-nitrogen compounds. The results provide material for a fairly detailed discussion of the boron-nitrogen bond from a structural-chemical viewpoint.

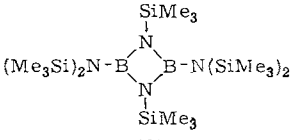
Compounds with tetravalent boron ("borazanes", "cycloborazanes", "amine-boronium salts") generally exhibit only slight variations in the B—N bond lengths; the mean value is 1.58 Å. Compounds in which the B—N bond is seriously weakened by steric or electronic effects represent excep-



(1)



(2)



(3)

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tions. Larger variations in B—N bond lengths are found when boron and nitrogen are in trigonal coordination, in agreement with the varying π-bonding component in such bonds. The shortest B—N bonds occur predictably in monoaminoboranes [1,3,5-tris(dimethylamino)-1,3,5-triboracyclohexane *(1)* 1.400 Å[1], dimethylaminodichloroborane 1.378 Å[2]]. When two or three nitrogens are bonded to one boron, and *vice versa*, the B—N bonds tend to be somewhat longer [*e.g.* borazine 1.435_5 Å[3], tris(dimethylamino)borane 1.431 Å[4], tris(1,3,5-benzodioxaborol-2-yl)-amine *(2)* 1.438 Å[5]].

Particular interest attaches to cyclic B—N compounds having further exocyclic nitrogens on the boron atoms. Whereas the 1.498-Å exocyclic B—N bond in monoaminoborazine is markedly longer than the bonds in the ring (1.418 Å[6]), both kinds of B—N bonds are of practically equal length in *B*-tris(dimethylamino)borazine (1.429 and 1.433 Å[7]) and in hexakis(trimethylsilyl)-2,4-diamino-1,3,2,4-diazadiboretidine *(3)* (1.441 and 1.454 Å[8]). This is surprising in compound *(3)* since the exocyclic Si_2N group are twisted by about 70° out of the plane of the ring owing to steric constraints. In contrast, the tris(dimethylamino)borazine molecule is almost completely planar.

The structural chemistry of the boron-sulfur bond has been far less thoroughly studied. Our own X-ray investigations are presently concerned with compounds of the type X_2BSR, XBS, and RSBS (X = halogen, NR_2; R = alkyl, H). On the basis of molecular weight determinations and molecular spectra, these compounds are described in the literature partly as dimers and partly as trimers; such statements, however, often lack a firm backing. As is clear from the chemistry of aluminum[9] the occurrence of polymeric structures must also be reckoned with in the solid state.

Lecture at Clausthal-Zellerfeld on January 15, 1971 [VB 294 IE]
German version: Angew. Chem. *83*, 505 (1971)

[1] *H. Hess*, Acta Crystallogr. *B 25*, 2334 (1969).

[2] *F. B. Clippard jr.* and *L. S. Bartell*, Inorg. Chem. *9*, 2439 (1970).

[3] *W. Harshbarger, G. H. Lee, R. F. Porter*, and *S. H. Bauer*, Inorg. Chem. *8*, 1683 (1969).

[4] *A. H. Clark* and *G. A. Anderson*, Chem. Commun. *1969*, 1082.

[5] *G. J. Bullen* and *P. R. Mallinson*, Chem. Commun. *1970*, 2213.

[6] *W. Harshbarger, G. H. Lee, R. F. Porter*, and *S. H. Bauer*, J. Amer. Chem. Soc. *91*, 551 (1969).

[7] *H. Hess* and *B. Reiser*, Z. Anorg. Allg. Chem. *381*, 91 (1971).

[8] *H. Hess*, Acta Crystallogr. *B 25*, 2342 (1969).

[9] *D. J. Brauer* and *G. D. Stucky*, J. Amer. Chem. Soc. *91*, 5462 (1969).

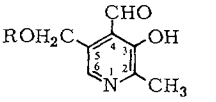
Dual Role of Pyridoxal 5′-Phosphate as Chemical and Conformation-Determining Active Group in Glycogen Phosphorylase

By *Ernst Helmreich*[*]

The first α-glucan phosphorylase shown to contain pyridoxal 5′-phosphate *(2)* was rabbit muscle phosphorylase a. Meanwhile pyridoxal 5′-phosphate has been found in all α-glucan phosphorylases. Removal of this group yields a crystalline, inactive apoenzyme[1]. In the rabbit, phosphorylase contains more pyridoxal 5′-phosphate than all the other pyridoxal 5′-phosphate-dependent enzymes together[2].

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The imine group linking the pyridoxal 5′phosphate to an ε-aminolysyl group of the phosphorylase protein can be reduced with $NaBH_4$. The resulting reduced phosphorylase still possesses about 60% of its original activity. This important experiment[3] shows that—in case pyridoxal 5′-phosphate should participate directly in phosphorolysis of the α−1→4 glycosidic bonds in glycogen—such a reaction



(1), R = H
(2), R = H_2O_3P

must follow a completely different course from all previously encountered enzyme catalyses involving pyridoxal 5′-phosphate. (In the other cases—transformations of amino acids—pyridoxal 5′-phosphate participates *via* its 4-formyl group.)

In aqueous solution, pyridoxal *(1)* and its analogs lacking the 5′-phosphate group exhibit a pH-dependent *intermolecular* proton transfer between nitrogen and the oxygen in position 3. In the case of pyridoxal 5′-phosphate and its analogs an additional *intramolecular* transfer occurs involving three proton-donor-acceptor groups[4]. In order to establish whether the pyridoxal 5′-phosphate in the phosphorylase also participates in an enzymatic acid-base catalysis as a "proton shuttle", the three protonatable groups were modified. Apart from the 3-*O*-methyl derivative, which has been synthesized and studied by *Pocker* and *Fischer*[5], and the *N*-oxide, previously obtained by *Fukui*[6], the monomethyl ester of pyridoxal 5′-phosphate and 3-*O*-methylpyridoxal 5′-phosphate *N*-oxide were synthesized for the first time and investigated. These analogs were bound stoichiometrically with sufficient affinity to the apoenzyme. The phosphorylases bearing these analogs have the same quaternary structure as the native active enzymes, but except for 3-*O*-methylpyridoxal 5′-phosphate-phosphorylase they were all inactive. The 20% activity of pyridoxal 5′-phosphate *N*-oxide-phosphorylase arises from deoxygenation of the *N*-oxide to pyridoxal 5′-phosphate by a cysteine group of the apophosphorylase[7].

To decide whether 1) the pyridinium nitrogen and/or the phosphate group participate as proton-donor-acceptor groups in catalysis, or whether 2) these groups induce a conformation of the active site that is necessary for catalysis, or 3) fulfill both functions, the pH-dependent fluorescence quantum yield of $NaBH_4$-reduced pyridoxamine compounds *(1)* and *(2)* and analogs covalently bonded to the enzyme was measured[9], using the method of *Cortijo* and *Shaltiel*[8]. Using this method and kinetic measurements of tritium-hydrogen exchange with phosphorylase[10] the search was opened for an analog-bearing enzyme having

[1] *T. Baranowski, B. Illingworth, D. H. Brown*, and *C. F. Cori*, Biochem. Biophys. Acta *25*, 16 (1957).

[2] *E. H. Fischer, A. Pocker*, and *I. C. Saari*, Essays in Biochem. *6*, 23 (1970).

[3] *E. H. Fischer, A. B. Kent, E. R. Snyder*, and *E. G. Krebs*, J. Amer. Chem. Soc. *80*, 2906 (1958).

[4] *M. L. Ahrens, G. Maas, P. Schuster*, and *H. Winkler*, FEBS-Lett. *5*, 327 (1969).

[5] *A. Pocker* and *E. H. Fischer*, Biochemistry *8*, 5181 (1969).

[6] *S. Fukui, N. Ohishi, Y. Nakai*, and *S. Shimizu*, Arch. Biochem. Biophys. *130*, 584 (1969).

[7] *Th. Pfeuffer, J. Ehrlich*, and *E. Helmreich*, unpublished.

[8] *M. Cortijo* and *S. Shaltiel*, Biochem. Biophys. Res. Commun. *39*, 212 (1970).

[9] *K. Feldmann, H. Winkler*, and *E. Helmreich*, unpublished.

[10] *D. Palm* and *D. Weisshaar*, unpublished.

the same, or at least a very similar, conformation of the active site as that of pyridoxal 5'-phosphate-phosphorylase. The inactive phosphorylase carrying the pyridoxal 5'-phosphate monomethyl ester exhibits the greatest similarity to the active enzyme. However, no proof has yet been obtained of any homology of conformation by hybridization of the active and the above inactive phosphorylase. Once such a proof has been obtained it may be assumed that the phosphorylase with the ester group is inactive because the phosphate group (pK 6.2) required for the chemical reaction—an acid-base catalysis—is blocked. Experiments to substantiate or disprove this assumption are in progress.

Lecture at Giessen on February 9, 1971 [VB 295 IE]
German version: Angew. Chem. *83*, 505 (1971)

Reactions at Coordinatively Unsaturated Surface Compounds

By *Hans L. Krauss*[*]

The phenomenon of the formation of "surface compounds" by reaction of "free" surfaces, and the special case of saturation of SiO_2 surfaces by the components of water (silica gel ≡polysilicic acid) have led us to a more detailed investigation of the reaction of such polysilicic acid with other acids, specifically with chromic acid. In favorable cases some 85% of the SiOH groups react and are involved in bichromate bridges. The upper limit for this anhydride formation, *i.e.*, formation of surface compounds, is set by the nature of the surface and the number of available OH groups; in favorable cases compounds containing *ca.* 6.5% of chromium are obtained.

Chromic polysilicic anhydride is stable up to *ca.* 1000 °C, but it is sensitive to reducing agents; *e.g.*, it can be reduced quantitatively to Cr(II) compounds by H_2, CO, or hydrocarbon vapors. CO is optimal for this reaction as it produces no water. The resulting Cr(II) surface compound is coordinatively unsaturated and correspondingly reactive and energy-rich, like a "naked" surface; it therefore tends to attain an energetically more favorable state either by reoxidation or by additional coordination.

The *reoxidation*, which occurs with O_2, halogens, NO, *etc.*, regenerates Cr(VI) compounds, a remarkable orange-red chemiluminescence (616 nm) occurring on reoxidation with oxygen. The Cr(II) compound provides an extremely good oxygen getter, the oxygen equilibrium pressure being 10^{-27} atm. (Cl_2 reacts analogously by way of a chromium(IV) compound to chromyl chloride.) Corresponding reactions have been observed with almost all the transition metals.

As "naked surfaces", the reduced surface compounds also seek to decrease their energy by coordination of further ligands. The Cr(II) compound reacts, for instance, with N_2, CO, NH_3, HCl, aromatic hydrocarbon vapors, olefins, *etc.*, yielding complexes. These adducts have been subjected to more detailed study by optical and gravimetric methods.

Complex formation of olefins is followed by polymerization; acetylene yields 1,3,5-substituted benzene derivatives.

The presence of three free coordination sites on the metal is postulated as required for the polycondensation reaction. Ethylene could then polymerize by a σ/π interchange mechanism; the primary formation of a π-complex containing two molecules of olefin would be followed by a disproportionation step (ethyl-Cr or H—Cr σ-bond). All the experimental data fit this hypothesis, *e.g.*, the formation of atactic polypropene from propylene and α-methyl ketones on use of ethylene as reducing agent.

Lecture at Berlin on February 4, 1971 [VB 296 IE]
German version: Angew. Chem. *83*, 507 (1971)

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Chromatographic Resolution of Racemates[**]

By *Gottfried Blaschke*[*]

Systematic investigation of chromatographic resolution of racemates on optically active adsorbents[1] has hitherto been hindered because detecting the resolution by optical rotation is insensitive and liable to interference. By using the double labeling technique we have developed a method of detection that can be carried out even with very small amounts of racemate. This method yields the ratio of enantiomers in each chromatographic fraction rapidly, accurately, and without interference by optically active impurities. Our test material was mandelic acid.

In each case we mixed equal amounts of optically pure[2] [^{3}H]-(*R*)-(−)-mandelic acid (20 μC/mg) and [^{14}C]-(*S*)-(+)-mandelic acid (1 μC/mg), which gave the doubly labeled test racemate; we diluted this with inactive, racemic mandelic acid and then carried out the chromatography. We were then able, by scintillation spectrometry, to determine the ^{3}H/^{14}C-ratio and thus both the ratio and the absolute concentrations of the two antipodes in the eluate.

In this way we studied the chromatographic resolution of mandelic acid on more than 50 optically active adsorbents whose chirality and functional groups were varied systematically. Because of the great sensitivity of the measurements, even 2—10 g of any one adsorbent sufficed for these studies. The optically active adsorbents used were prepared as follows: 1) By treating optically active alcohols or amines with crosslinked or non-crosslinked poly-

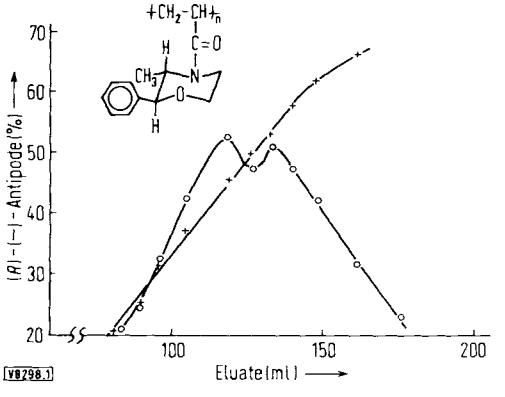


Fig. 1. Chromatographic resolution of 3.9 mg of racemic mandelic acid on 5.1 g of the polyacrylamide from *trans*-(2*S*,3*S*)-2-methyl-3-phenylmorpholine. Column 11.2 × 1.2 cm. Eluant benzene-dioxane 95:5. —o—o—o— rel. concentration of mandelic acid; ×—×—×— content of (*R*)-(−)-antipode.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

acryloyl chloride; 2) by treatment of optically active amino esters and tertiary amines with crosslinked chloromethylated polystyrene; and 3) by polymerization of optically active acrylic esters and amides.

Resolution was studied in each case with 1—10 mg of doubly labeled racemic mandelic acid on 10-cm columns. With almost all the adsorbents enrichment of one antipode was definitely detectable, at least in the first and last fractions of the eluate. With cinchonine polyacrylate prepared by method (1) it amounted to 18%, the (*R*)-(−)-antipode being enriched in the first fractions. The separation on ephedrine esters [*N*-benzylephedrine polyacrylate 30%, (*S*)-(+)-antipode eluated first] was even more marked and could be further improved if the chiral center were built into a rigid skeleton (Fig. 1).

It is remarkable that the elution profile shows two maxima. By using longer columns of the synthetic adsorbents it is now possible for the first time to resolve racemates quantitatively. Further, the second racemate tested by us, namely, methyl mandelate, is also partly separated into its antipodes on the adsorbents reported above.

Lecture at Kiel on February 11, 1971 [VB 298 IE]
German version: Angew. Chem. *83*, 547 (1971)

[1] For a review see *G. Losse* and *K. Kuntze*, Z. Chem. *10*, 22 (1970).

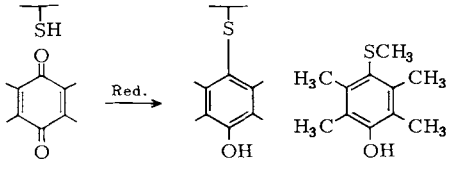
[2] Radiochemical and optical purities were proved by isotope dilution analysis. Reproducible results were also obtained with the test racemate [^{3}H]-(*S*)-(+)-mandelic acid/[^{14}C]-(*R*)-(−)-mandelic acid. Isotope effects thus did not interfere.

Model Reactions for Oxidative Phosphorylation: Sulfur Compounds as Carriers of the Phosphoryl Group

By *Edmund Bäuerlein* and *Theodor Wieland*[*]

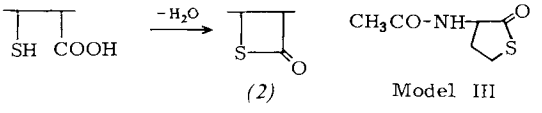
For more than ten years *Th. Wieland*'s school have ascribed particular importance to mercapto groups for transfer of the phosphoryl group[1]. Butyl thiophosphate, $C_4H_9S—PO_3^{2\ominus}$, had been synthesized and studied as a model for a sulfur-containing coenzyme phosphate, CoA phosphate[2].

Reaction between one member of the electron-transport chain and the mercapto groups of proteins can lead to *p*-(alkylthio)phenol (*S*-alkylmonothiohydroquinone) *(1)*[3].



(1) Model II

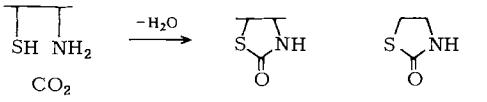
Functional groups such as carboxyl and mercapto attached to the protein may react with each other to give cyclic thioesters of type *(2)*[4].



(2) Model III

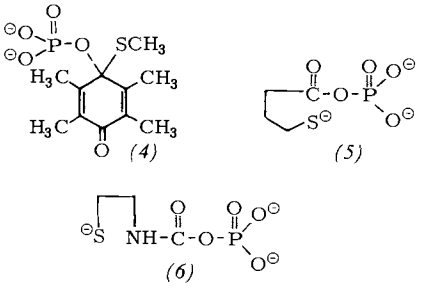
[*] Dr. E. Bäuerlein and Prof. Dr. Th. Wieland
Max-Planck-Institut für medizinische Forschung,
Abteilung Chemie
69 Heidelberg, Johnstrasse 29 (Germany)

Mercapto and amino groups attached to a protein can react with CO_2 to give cyclic carbamic thioesters of type *(3)*[5].



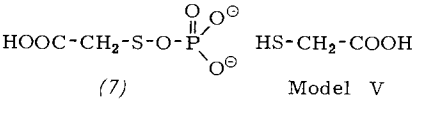
(3) Model IV

If the model compound II, III, or IV is oxidized with bromine in anhydrous pyridine in presence of ADP and phosphate, then high yields (27—38%) of ATP are obtained by way of the unisolable, high-energy, phosphorylated compounds such as the quinol phosphate *(4)*, the acyl phosphates *(5)*, or the carbamoyl phosphates *(6)*.

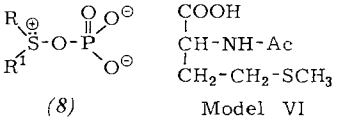


(4) *(5)* *(6)*

In the same system a new type of reaction was discovered, namely, direct oxidation of a mercapto compound, specifically mercaptoacetic acid[6] (model V, 34% of ATP). The mixed anhydride *(7)* of sulfenic and phosphoric acids must be assumed as the high-energy phosphorylated compound. *Lambeth* and *Lardy*[7] used a thioether (sulfide), namely, *N*-acetylmethionine (model VI) in the same system (36% of ATP); *(8)* is presumably the high-energy phosphorylated intermediate.



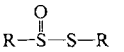
(7) Model V



(8) Model VI

As a model for cytochromes, hemin[8] was used successfully as oxidant of the mercaptoacetic acid (15% of ATP), which was the most effective of the mercapto compounds tested for ATP formation[9]. Thiols are better mediators than H_2S or sulfides.

Our investigations with a lipophilic medium showed that the yield of ATP obtained on oxidation of mercaptoacetic acid by hemin is appreciably increased[9] (22% of ATP) by the presence of its disulfide, dithiobis(acetic acid). Unexpectedly, oxidation of the disulfide alone (in presence of ADP and phosphate) also led to synthesis of ATP (13.7%); the thiosulfinate (disulfide monoxide)



can be assumed to be the first product of this oxidative phosphorylation.

Comparative experiments in an atmosphere of oxygen or nitrogen showed that there was pronounced oxygen-dependence of ATP formation in all the hemin experiments made[10]. Thus our results indicate that, rather than the monomeric cytochrome c, the cytochrome-c oxidase which probably has quaternary structure is the site of the redox reaction between mercapto groups and two groups of hemin compounds (cytochrome a and a_3).

Lecture at Dortmund on January 25, 1971 [VB 297 IE]
German version: Angew. Chem. *83*, 506 (1971)

[1] *Th. Wieland* and *E. Bäuerlein*, Naturwissenschaften *54*, 80 (1967).
[2] *Th. Wieland* and *R. Lambert*, Chem. Ber. *89*, 2476 (1956).
[3] *Th. Wieland* and *E. Bäuerlein*, Monatsh. Chem. *98*, 1381 (1967).
[4] *Th. Wieland* and *E. Bäuerlein*, Chem. Ber. *100*, 3869 (1967).
[5] *Th. Wieland* and *H. Aquila*, Chem. Ber. *101*, 3031 (1968).
[6] *Th. Wieland* and *E. Bäuerlein*, Angew. Chem. *80*, 915 (1968); Angew. Chem. internat. Edit. *7*, 893 (1968).
[7] *D. O. Lambeth* and *H. A. Lardy*, Biochemistry *8*, 3395 (1969).
[8] *E. Bäuerlein* and *Th. Wieland*, Chem. Ber. *103*, 648 (1970).
[9] *E. Bäuerlein* and *Th. Wieland*, Proceedings of the Colloquium on Bioenergetics, Bari, Sept. 1970: "Energy transduction in respiration and photosynthesis".
[10] *E. Bäuerlein*, *Th. Wieland*, and *M. Klingenfuß*, J. Europ. Biochem., in preparation.

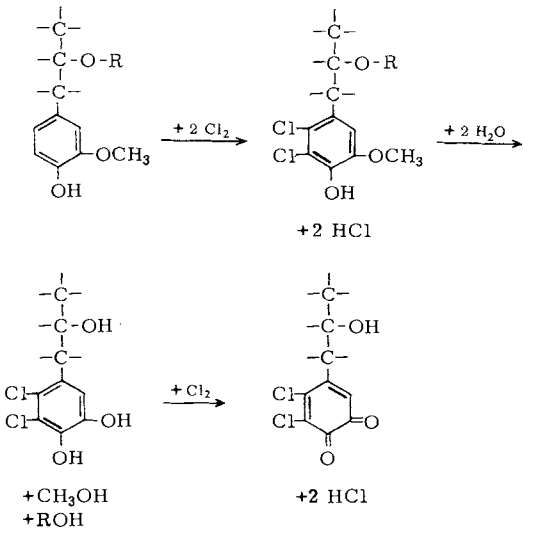
The Chemistry of Lignin-removing Bleaching

By *Thomas Krause*[*]

Lignin-removing bleaching of cellulose pulps is usually carried out in several stages. The bleach sequence consists, in principle, of a chlorination stage (which leads to partial degradation of the lignin to alkali-soluble products), alkaline extraction of the degradation products, and one or several oxidative stages in which hypochlorite and/or chlorine dioxide is used as bleaching agent. The following details are extracted from the voluminous literature on the reactions of lignin and carbohydrates in the individual bleaching stages:

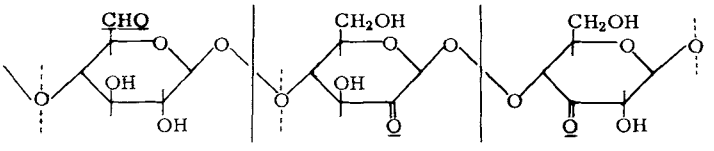
The chlorination stage leads, when chlorine water (pH = 1.5 to 2.0) is used, to colored *o*-quinonoid compounds owing to chlorination of the phenylpropane units of lignin at positions 5 and 6, followed by hydrolysis of ether linkages both on the aromatic ring and in the aliphatic side chains.

Further amounts of chlorine are consumed in slow oxidative reactions that probably cause fission of C—C bonds between the phenylpropane units or removal of aliphatic side chains. These reactions occur in that way only if the aromatic ring does not contain other 5- or 6-substituents and if the phenolic hydroxyl groups are not etherified. The lignin molecule is cleaved by these reactions into alkali-soluble fragments. The residual lignin in the cellulose pulp is highly condensed. The subsequent hypochlorite bleaching stage causes only very little chlorination. Oxidations lead first to *o*-quinonoid structures; if further favored by use of higher temperatures, however, they proceed until the aromatic nucleus is degraded to CO_2 and organic acids (*e.g.*, oxalic and maleic acid).



R = phenylpropane unit.

Bleaching by chlorine dioxide takes a similar course. This bleaching agent has the advantage that it does not attack carbohydrates. Treatment with either chlorine or hypochlorite degrades the carbohydrates (cellulose and hemicelluloses) by oxidation. The keto groups at position 2 and/or 3, or the aldehyde groups at position 6, formed in the carbohydrate monomers, cause labilization of the β-



——: oxidized group; ¦ alkali-labile bond.

glucosidic bond to alkali and shortening of the chain by hydrolytic fission of these bonds in the alkaline medium.

Partial inhibition of carbohydrate degradation can be achieved by small additions of chlorine dioxide at the chlorination stage or of sulfamic acid at the hypochlorite stage.

Lecture at Darmstadt on March 5, 1971 [VB 299 IE]
German version: Angew. Chem. *83*, 548 (1971)

Problems and Results in the Chemistry of Peroxosilicon and Peroxosulfur Compounds

By *Armand Blaschette*[*]

1. Cleavage of benzil and substituted benzils by H_2O_2, which is known to depend on nucleophilic attack by HO_2^- on a carbonyl-carbon atom of the α-diketone, is specifically catalyzed by alkali-metal silicates in aqueous solution at pH > 7. Kinetic analysis of the catalyzed reaction, and in particular the discontinuous pH-dependence of the catalysis constant, shows that the catalytic effect is to be ascribed to formation of several peroxosilicate species in different

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states of substitution and/or protonation and having different nucleophilic reactivities in equilibria of the type

$$(HO)_3SiO^- + HO_2^- \rightleftharpoons (HO)_2(HOO)SiO^- + HO^-$$

2. Stable sodium ethoxoperoxosilicates having the analytical composition

$$(Na^+)_x[(OO)_x(HOO)_{n-x}Si(OC_2H_5)_{4-n}]^{x-}$$

are obtained by perhydrolysis of tetraethoxysilane with 100% H_2O_2 in anhydrous ethanol in the presence of sodium ethoxide and these may contain up to 44% of peroxidic oxygen (corresponding to, *e.g.*, $x=2$, $n=3$) according to the molar ratio $Si(OC_2H_5)_4:H_2O_2:NaOC_2H_5$ used. The matter of the chemical homogeneity of these peroxosilicates requires further investigation.

3. The very reactive trimethylsilyl peroxosulfates

$$(CH_3)_3SiOSO_2OOSi(CH_3)_3 \text{ and } (CH_3)_3SiOSO_2OOSO_2OSi(CH_3)_3$$

which are unstable at 20 °C are formed on treatment of bis(trimethylsilyl) peroxide with SO_3 in the molar ratio 1:1 or 1:2, respectively, in CH_2Cl_2 at −30 to −20 °C.

Dibutyl peroxide and SO_3, however, give only adducts[1].

4. $K_2S_2O_8$ and $[(C_6H_5)_4As]_2S_2O_8$ react with SO_3 in CH_2Cl_2 (molar ratio 1:2) in a heterogeneous reaction to give monoperoxotetrasulfates $K_2S_4O_{14}$ and $[(C_6H_5)_4As]_2S_4O_{14}$ quantitatively. If this reaction is carried out with the molar ratio 1:1, equimolar mixtures of monoperoxotetrasulfates and unchanged peroxodisulfate are formed instead of the expected monoperoxotrisulfate $M_2S_3O_{11}$[2]. Experiments in which $^{35}SO_3$ is used show that formation of $S_4O_{14}^{2-}$ from $S_2O_8^{2-}$ and SO_3 does not occur exclusively by addition of SO_3 molecules to terminal oxidic oxygen atoms of the peroxodisulfate anion but that part of the SO_3 is inserted into the S—OO bonds of the $S_2O_8^{2-}$[3].

5. Alkyl sulfamoyl peroxides—representatives of a new class of compound—are obtained in diethyl ether at −40 °C as follows:

$$ROOH + ClSO_2NH_2 + C_5H_5N \rightarrow ROOSO_2NH_2 + [C_5H_5NH]Cl$$

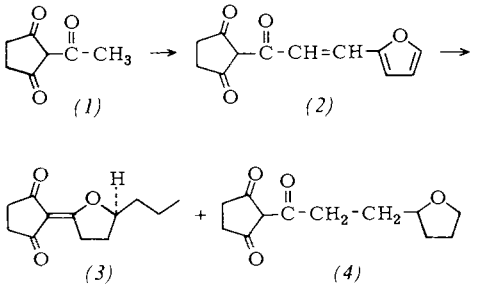
Above −10 °C they decompose rapidly by heterolysis of the O—O bond. The following decomposition products have been isolated so far: (a) R = propyl: sulfamic acid, propanal, propyl and isopropyl propionate; (b) R = butyl: sulfamic acid, butanal, isobutanal, and butyl butyrate; (c) R = *tert*-butyl: acetone and *tert*-butyl acetate.

Lecture at Düsseldorf on March 8, 1971 [VB 300 IE]
German version: Angew. Chem. *83*, 548 (1971)

[1] *B. Bressel* and *A. Blaschette*, Z. Anorg. Allg. Chem. *377*, 182 (1970).
[2] *B. Bressel* and *A. Blaschette*, Z. Anorg. Allg. Chem. *377*, 162 (1970).
[3] *A. Blaschette* and *B. Bressel*, Z. Anorg. Allg. Chem. *377*, 174 (1970).

SELECTED ABSTRACTS

The structure and synthesis of oudenone, a novel tyrosine hydroxylase inhibitor which was recently discovered in the culture filtrate of *Oudemansiella radicata*, is the subject of a report by *M. Ohno, M. Okamoto, N. Kawabe, H. Umezawa, T. Takeuchi, H. Iinuma*, and *S. Takahashi*. Oudenone, m. p. 77–78 °C, $[\alpha]_D^{21} = -10.8°$ (ethanol) has the structure *(3)*. Condensation of 2-acetyl-1,3-cyclopentanedione *(1)* with furfural gave *(2)*, which on hydrogenation with Pt/H_2 in presence of NaOH afforded the products *dl-(3)* and *(4)*.

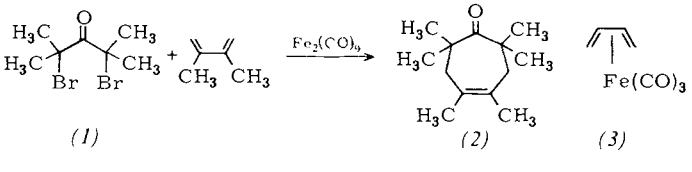


(1) *(2)* *(3)* *(4)*

Racemic *(3)* was resolved with brucine hydrate. *(3)* exhibits a blood pressure reducing effect. / J. Amer. Chem. Soc. *93*, 1285 (1971) / –Ma.

[Rd 359 IE]

The synthesis of seven-membered carbocyclic ketones and troponoid compounds has been accomplished by *R. Noyori, S. Makino*, and *H. Takaya* by dehalogenation of α,α'-dibromoketones with carbonyliron compounds in the presence of 1,3-dienes. For example, when a solution of 2,4-dibromo-2,4-dimethylpentan-3-one *(1)*, $Fe_2(CO)_9$, and 2,3-dimethylbutadiene in dry benzene was heated (60 °C, 40 h, N_2), 2,2,4,5,7,7-hexamethyl-4-cycloheptenone *(2)* was obtained in 71% yield. Butadiene, isoprene, and cyclopentadiene afford similar adducts. Notably increased

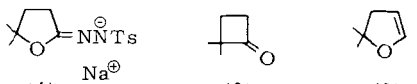


(1) *(2)* *(3)*

yields of cycloheptanones were obtained when the butadiene tricarbonyliron complex *(3)* was used in place of $Fe_2(CO)_9$. 4-Cycloheptenones derived from *sec*-bromides and open-chain 1,3-dienes can be converted into troponoid compounds. The mechanism of the annelation reaction is still unclear. / J. Amer. Chem. Soc. *93*, 1272 (1971) / –Ma.

[Rd 360 IE]

The rearrangement of a thermally generated oxycarbene has been investigated by *W. C. Agosta* and *A. M. Foster*. Thermal decomposition of the dry Na salt *(1)* of 4-hydroxy-4-methylvaleric acid γ-lactone tosylhydrazone at 310 °C/0.1 torr led to volatile products (*ca.* 45% of theory) from



(1) *(2)* *(3)*

which 2,2-dimethylcyclobutanone *(2)* (70%) and 2,2-dimethyl-2,3-dihydrofuran *(3)* (30%) could be separated by gas-liquid chromatography. / Chem. Commun. *1971*, 433 / –Ma.

[Rd 361 IE]

Organoelementphosphanepentacarbonyl-chromium, -molybdenum, and -tungsten complexes have been synthesized by *H. Schumann, O. Stelzer, J. Kuhlmey*, and *M. Niederreuther* by UV irradiation of THF solutions of the hexacarbonylmetal compounds in the presence of the substituted phosphanes:

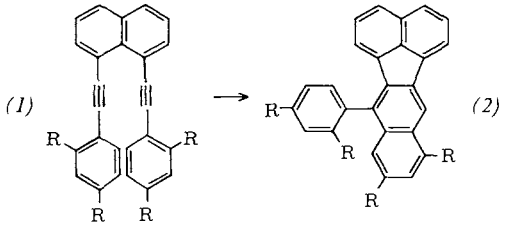
$$(CO)_6M + P[El(CH_3)_3]_3 \xrightarrow{h\nu} (CO)_5MP[El(CH_3)_3]_3 + CO$$

M = Cr, Mo, W; El = C, Si, Ge, Sn.

Only the complexes with M = Mo, El = Si and M = W, El = Si could be isolated in very pure form. The new compounds are yellow, stable towards air and water, and are remarkably thermally stable. Their IR, UV, ^{1}H-NMR, and ^{31}P-NMR spectra are discussed in detail. / Chem. Ber. *104*, 993 (1971) / –Kr.

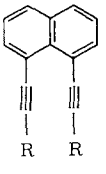
[Rd 364 IE]

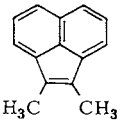
Intramolecular interactions between parallel triple bonds have been studied by *H. A. Staab, J. Ipaktschi*, and *A. Nissen*. The compounds chosen for investigation were the 1,8-bis(arylethynyl)naphthalenes *(1)*, the 1,8-bis(1-alkynyl)-naphthalenes *(3)*, and the tetradehydrodinaphthocyclodecene *(5)*. No strong interaction of the triple bonds could be inferred from the spectra of *(1)* and *(3a)*; however,



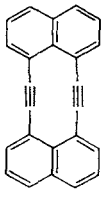
(1) *(2)*

(3a), R = H
(3b), R = CH_3
(3c), R-R = $-(CH_2)_3-$

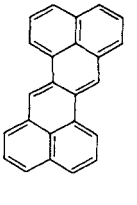




(6a)



(5)

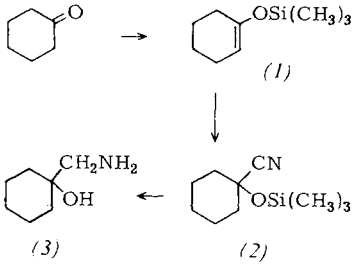


(6)

reactions of *(1)* and *(3a)*, *e.g.* isomerization to *(2)* and hydrogenation with Lindlar catalyst to *(4a)* respectively, are largely determined by these bonds. *(3c)* is considerably more reactive than *(3b)* because its pair of triple bonds are restricted from orienting themselves into a position of non-interference. In attempts to synthesize *(2)* by coupling 1-ethynyl-8-iodonaphthalene as the copper acetylide, dibenzonaphthacene *(6)* was formed instead. / Chem. Ber. *104*, 1170, 1182, 1191 (1971) / –Kr.

[Rd 365 IE]

β-Amino alcohols such as *(3)* have been prepared by *W. E. Parham* and *C. S. Roosevelt* by a new route from ketones such as cyclohexanone. Anhydrous HCN was added to the trimethylsilyl ether *(1)* of the corresponding enol to give the cyanide *(2)*, which, after reduction of the nitrile



(1) *(3)* *(2)*

group and hydrolysis of the trimethylsilyl group, afforded the β-amino alcohol *(3)*. The method is particularly suitable for sterically hindered ketones, *e.g.* 1,2,3,4,4a,9a-hexahydro-9-fluorenone. / Tetrahedron Lett. *1971*, 923 / –Kr.

[Rd 366 IE]

The nature of the rotational barrier in acetaldehyde has been investigated by *R. B. Davidson* and *L. C. Allen*. With the aid of SCF—MO calculations they analyzed the changes of attractive and repulsive forces between non-bonded atoms on rotation about the C—C bond. The calculated rotational barrier (1.09 kcal mole^{-1}) is in good agreement with the experimental one (1.16 kcal mole^{-1}). In acetaldehyde, the attraction between methyl H and O dominates the barrier, whereas in ethane H—H repulsion is the most important factor. The balance of attractive and repulsive potentials between non-bonded atoms is further discussed considering substituent effects on rotational barriers. It is stressed that the neglect of attractive interaction is a serious defect of simple models of hindered rotation. / J. chem. Physics *54*, 2828 (1971) / –Hz.

[Rd 371 IE]

The catalytic activity of palladium in acetylene hydrogenation has been studied by *Y. Inoue* and *I. Yasumori*. There are conspicuous differences in activity between Pd foils annealed at less than 200 °C (L) or above 800 °C (H) after cold-working. The overall activity of L foils is considerably larger than that of H foils, but the product ratio ethylene/ethane is about 30 for H foils and less than 15 for L foils. Fast changes in H_2 pressure during the reaction effects a rapid response in reaction rate on L foils; on H foils the rate changes slowly during a transition period of up to 1 h. Similar differences in response are observed on rapid displacement of H_2 by D_2. It is concluded that L catalyst works by adsorption of hydrogen on its surface, whereas the activity of H catalyst is due to hydrogen absorption in the bulk of the metal. / J. physic. Chem. *75*, 880 (1971) / –Hz.

[Rd 369 IE]

The reactions of triallylchromium(III) and of tetraallyldichromium(II) with 2-butyne have been investigated by *R. P. A. Sneeden* and *H. H. Zeiss*. The catalytic activity of triallylchromium in the polymerization of olefins is already well-known. Both chromium compounds mentioned were allowed to react with 2-butyne under identical conditions; in each case the same four products were obtained, but in different relative amounts. (1,2,3,4-Tetramethyl-, pentamethyl-, and hexamethylbenzene, along with traces of 1,2,3,5-tetramethylbenzene.) Allyl groups originally bonded to chromium are not involved in product formation except in the case of hexamethylbenzene. The mechanisms of these reactions remain unexplained. / J. Organometal. Chem. *28*, 259 (1971) / –Ee.

[Rd 368 IE]

For the IR analysis of gas mixtures a modified matrix isolation method is suggested by *M. M. Rochkind*; it is called pseudo matrix isolation (PMI) by the author. The gas is diluted 1:100 with nitrogen, and the mixture is frozen in "pulses" of 0.1 to 0.5 mmoles onto an IR transmitting substrate cooled by liquid H_2. The technique compares favorably with conventional IR methods of gas analysis since rotational structure of gas spectra is suppressed and intermolecular interactions modifying the characteristic frequencies in pure frozen gases are virtually eliminated. The method is suitable for qualitative and quantitative analyses; detection limits of 0.05 μmoles per cm^2 covered with the frozen mixture are not uncommon. / Spectrochim. Acta *27 A*, 547 (1971) / –Hz.

[Rd 370 IE]

BOOK REVIEWS

Physikalische Chemie (Physical Chemistry). By *E. A. Moelwyn-Hughes*, edited and translated by *W. Jaenicke* and *H. Göhr*, with the special assistance of *H.-D. Sabel*. Georg Thieme Verlag, Stuttgart 1970. 1st ed., 714 pp., 269 Figs., 309 Tables. DM 59.80.

The German translation of the second English edition of the well-known book by *Moelwyn-Hughes* is very different in structure from the textbooks on physical chemistry that have been used until now in German universities. The first five chapters (about 150 pages) deal with the principles of the kinetic theory of gases, quantum theory, and chemical thermodynamics. Separate chapters are devoted to the intermolecular energy and partition functions. Considerable space (about 100 pages) is allotted to monatomic, diatomic, triatomic, and polyatomic molecules, including the discussion of light dispersion, light absorption, the Raman effect, and X-ray and electron scattering. Chapters 12 to 17 (about 200 pages) deal with the states of matter (crystalline state, gaseous state, metallic state, liquid state, solutions, ions). The chapter on interfacial phenomena is followed by the discussion of the chemical equilibria in homogeneous systems and of the equilibria in heterogeneous systems, which also embraces phase equilibria and electromotive forces. The last three chapters, which occupy about 100 pages, deal with kinetics. Some mathematical problems are discussed in an Appendix.

This arrangement of the material has both advantages and disadvantages. The reader who has already been introduced to physical chemistry will welcome the self-contained treatment of the monatomic or polyatomic molecules, the states of matter, or kinetics. He will learn much from seeing how many problems can be solved by simple models with the aid of statistics or how various theories are used in attempts to deal with a given problem. While the beginner will find the first five chapters relatively easy to understand, he will have difficulty in recognizing the relations between the various thermodynamic equations derived, since items that belong together are often necessarily situated far apart because of the arrangement of the book.

An excellent introduction to the use of statistical thermodynamics is offset by a quantum-mechanical treatment of the chemical bond that is too brief by present-day standards.

Very commendable features are the numerous references and the many exercises, which include not only calculations but also many questions designed to test the student's understanding.

The book would probably make excessive demands on the beginner, but it is a true mine of information for the advanced student.

Gerd Wedler [NB 952 IE]

Undergraduate Instrumental Analysis. By *J. W. Robinson*. Marcel Dekker, Inc., New York. 1st Edit., 379 pp., *ca.* DM 44.—.

During the past decade the methods of instrumental analysis – in particular absorption spectroscopy in the IR, UV, and visible ranges, NMR spectroscopy, mass spectrometry, and gas chromatography – have become a fundamental part of inorganic and organic chemistry. Nevertheless, up to the present no generally accepted methods have been developed in West Germany for the teaching of these techniques.

The present book attempts, with considerable success from the instructional point of view, to present instrumental analysis to the beginner along the lines of "What is instrumental analysis?" After a general introduction (survey of analytical methods, observation of errors, sample handling, *etc.*), the book gives an introduction to spectroscopy and the basic principles of spectrometric systems. Then follow chapters on NMR, IR, and Raman spectroscopy, UV absorption spectroscopy, atomic absorption, colorimetry and polarimetry, flame photometry, emission spectroscopy, X-ray spectroscopy, chromatography, thermal analysis, mass spectrometry, and electrochemistry. In each chapter the theoretical and practical principles of the method are described, and an indication is given of the range of applications on the basis of simple and (in general) well chosen examples. Each chapter

closes with a bibliography, notes on instructive experiments for the reader to perform in order to drive home what he has learnt, and problems. The material is extremely well arranged, and the illustrations (as far as equipment is concerned, at any rate) are useful for teaching purposes.

To whom could this book be recommended? Only students in their first year, who are studying instrumental analysis as such within the framework of a general chemistry course or of specific lectures and practical sessions, but who are not interested in the individual techniques. The very number of methods treated shows that with its 379 pages this book can only be regarded as an introduction; thus, the chapter on mass spectrometry occupies only 17 pages. A student involved in practical work in inorganic, organic, or physical chemistry, who wants to know only about the methods of specific interest to himself (*e.g.* mass spectrometry, IR, UV, and NMR spectroscopy) and their possible range of applications, will reject the book as "too elementary" and turn to more reasonably priced handbooks. Students of biology, medicine (clinical chemistry), and members of the academic profession, who only require a superficial knowledge of the individual methods of instrumental analysis will find the book's approach admirably suited to their requirements.

The book can be heartily recommended to all concerned with the teaching of instrumental analysis, for this is a truly impressive demonstration of how even complicated theoretical and practical principles can be presented simply and in the way most suitable for teaching purposes.

Egon Fahr [NB 964 IE]

4. AUG. 1971

Non Aqueous Solvents. By *T.C. Waddington.* Studies in Modern Chemistry Series, edited by *W.C. Agosta* and *R.S. Nyholm.* Thomas Nelson and Sons Ltd., London 1969, 1st Edit., 88 pp., DM 22,—.

The selected ranks of this series, aimed particularly at advanced students, where each volume reflects the latest situation in its own speciality, are now joined by a new work on non-aqueous ionizing solvents. The author has considerable experience in this field, not only from his own research on anhydrous liquid hydrogen halides and anhydrous sulfuric acid but also as the editor of a collective work (Non Aqueous Solvent Systems. Academic Press, London and New York 1965).

The book deals on the one hand with solvents similar to water, *i.e.* weakly self-dissociating protonic solvents such as ammonia, hydrogen fluoride, and sulfuric acid in Chapter 2 and aprotic solvents such as the arsenic halides, antimony trichloride, iodine monochloride, and bromine trifluoride in Chapter 5; on the other hand, it also discusses solvents that do not resemble water so closely, since they either hardly dissociate of themselves at all, such as dinitrogen tetroxide and sulfur dioxide in Chapter 3 and the oxide-halides nitrosyl chloride and phosphorus oxychloride (Chapter 4), or are practically completely dissociated, such as the molten salts (Chapter 6). Wherever possible, the solvents are compared with one another within each chapter. The general ideas are summarized in Chapter 1, which serves as an introduction.

The author does not aim at a complete survey of the material concerned, but rather, by means of selected examples, at a complete review of the principles governing the behavior of ionizing non-aqueous solvents. From the viewpoint of coordination chemistry, this is most successful. However, the Brønsted and Lewis theories for the acid-base behavior of protonic and aprotic solvents are given extremely scanty treatment, and the solvent theory, which has rendered such important service in the development of the chemistry of water-like solvents, is not even mentioned.

The author follows an old-established practice in not quoting original papers but rather reviewing articles from monographs. This, together with the well thought out problems at the end of each chapter, emphasizes the fact that this volume is the instruction manual of choice for anyone looking for an introduction to ionizing non-aqueous solvents.

Jochen Jander [NB 966 IE]

Die Physik. Ihre Sprache und Untersuchungsmethoden (Physics. Its Language and Methods of Investigation) by *K. Kramer* and *K. Lüders.* Verlag Chemie, Weinheim 1970. 1st Edit., viii, 157 pp., 102 figures, 12 tables, bound, DM 22.50.

We are told in the foreword that the book is based on a series of university extension courses. The authors begin with an introduction to some fundamental concepts which they discuss with reference to selected subject areas (electron guns, optics of charged particles, vacuum, low temperatures, high magnetic fields, particle accelerators, electron spin resonance, nuclear spin resonance, structural analysis, and conductivity). They go on to give the reader an outline of the modern investigation methods used in physics. Naturally enough, within the scope of such a book it is impossible to proceed beyond the basic principles of the chosen subjects. The authors have succeeded in presenting a vivid impression of the wide range of modern methods of investigation. An evident desire always to press on quickly to topical problems is no doubt responsible for the fact that even relatively complicated quantitative relationships are sometimes presented in a highly concise form. To derive full benefit from the book it is desirable that the reader should already have acquired some knowledge of physics, or that he should be in the process of doing so within the framework of an appropriate course of study.

Werner Buckel [NB 967 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry), 8th fully revised edition. Published by the Gmelin-Institut für anorganische Chemie und Grenzgebiete in der Max-Planck-Gesellschaft zur Förderung der Wissenschaften under the direction of *Margot Becke-Goehring.* Verlag Chemie GmbH, Weinheim/Bergstr.[1].

System No. 49: Niobium. Part A.

Historical, Occurrence. The Element. Principal editor: *Herbert Lehl.* 1969. iv, xvi, 356 pp., 76 figures, linen. DM 426.—.

The first chapter of Part A presents the absorbing history of the discovery of niobium and the naming of the element. It was not until 1949 that the name was finally settled by a IUPAC decision in Amsterdam. A short paragraph on the physiological effects of niobium (with the rather vague observation that the toxicity of metallic niobium may be assumed to be similar to that of vanadium, and yet experiments are then described that gave no indication that niobium has a toxic action) and its compounds is followed by a chapter on the industrial preparation of the raw

[1] Cf. Angew. Chem. internat. Edit. *10*, 204 (1971).

materials. Special technical difficulties are encountered in the separation of the elements niobium and tantalum.

The remainder of the volume describes, in almost 330 pages, the preparation and the physical and chemical properties of the element, which is obtained by reduction of the oxides, halides, and oxide halides or by electrolytic methods. The growing importance of niobium as a material can be seen from the space devoted to the description. The use of niobium as the metal in electrical engineering and in reactor construction has necessitated an increase in production by more than 1000% over the past 10 years. New uses are also continuously being found for niobium compounds. Niobium hydride, which has a higher H density than water, is a useful neutron moderator. Niobium oxides are used as electrical resistors, ferroelectrics, piezoelectrics, catalyst materials, fluxes, *etc.*, Niobium nitrides, niobium borides, and niobium carbides are used as electrical resistors. Niobium carbides are also used as "hard metals". Considerable space is devoted to the 14 isotopes of niobium, their enrichment, and their separation.

Because of the metallurgical importance of niobium, the crystallographic, mechanical, electrical, and magnetic properties of the element have been intensively studied. This is true in particular of its superconductivity (superconductor of the 2nd type). Of all elements, niobium has the highest jump-temperature, *i.e.* 9.49 °K for highly purified niobium. The 26 pages devoted to the chemical behavior of the element are again a reflection of the increasing use of niobium as a material.

The remaining 40 pages of the volume deal with the detection and determination of the element. The articles that have been published since 1950, on detection and the special methods of detection and determination of the element, and those that have appeared since 1955, on determination and separation, are grouped and listed in a very clear manner.

The literature is covered in full up to the end of 1965, and in part up to 1968. It should be pointed out that the volume contains very large quantities of information taken from literature that is not easily accessible.

System No. 49: Niobium. Part B 1.

Compounds up to Niobium and Bismuth. Principal editor: *Herbert Lehl.* 1970. vi, xxvi, 424 pp., 121 figures, linen DM 515.—.

Whereas Part A, which deals with the element, is of particular interest to physicists, metallurgists, and engineers, Part B, of which this is the first volume, will appeal mainly to the chemist, though the compounds of niobium also include substances that are of physical and technical interest now, and will probably be even more so in the future (see the review of Part A). These will undoubtedly include the compounds in the niobium-nitrogen system, in which superconducting high-temperature phases having the approximate composition NbN occur.

In accordance with the Gmelin system, however, the compounds with hydrogen and oxygen are discussed first in the present volume. The niobium-oxygen system is extremely rich in phases. The discussion of the niobium-nitrogen compounds, which were briefly mentioned above, is followed by the chemistry of the niobium fluorides, chlorides, bromides, and iodides. The niobium-halogen systems are extremely rich in nonstoichiometric compounds, which result from the tendency of the element to form cluster ions such as $[Nb_6Cl_{12}]^{n+}$ or $[Nb_6Br_{12}]^{n+}$ containing niobium-niobium bonds. These cluster ions, the structure of which has only recently been elucidated, are described jointly for the systems Nb—Cl and Nb—Br. Structural groups containing Nb—Nb bonds, such as $[Nb_6I_8]$ or $[Nb_2I_8]$, are also found in the niobium-iodine system.

Among the niobium(v) oxide chlorides $NbOCl_3$, NbO_2Cl, $Nb_4O_9Cl_2$, and Nb_3O_7Cl described in the literature, it is probable that only $NbOCl_3$ exists as an equilibrium phase in the system $NbCl_5$—Nb_2O_5. In the niobium-sulfur system, which is described next, there are subsulfides $Nb_{1+x}S$, monosulfides $Nb_{1-x}S$, sesquisulfides $Nb_{1+x}S_2$, disulfides, and trisulfides. Niobium atoms are also linked directly to one another in the niobium(IV) sulfide halides, *e.g.* the compound NbS_2Cl_2. The extremely large number of phases is again striking in the niobium-selenium and niobium-tellurium systems.

The niobium-boron system, which is discussed in the next section, is characterized by two congruently melting phases NbB_2 and NbB, two incongruently melting phases Nb_3B_4 and Nb_3B_2, and two eutectics. Apart from their industrial importance, the niobium borides are interesting from the standpoints of lattice structure, electronic structure, and chemical bonding. Bonding relations of similar complexity are also found for the carbides and silicides of niobium. The chapter on niobium-carbon is confined to the systems Nb—C, Nb—C—O, Nb—C—N, Nb—C—N—O, and Nb—C—B—(N), whereas salts of organic acids, carbonyl compounds, organoniobium compounds, and coordination compounds are discussed in Volume B 3.

The niobium-silicon chapter deals not only with the niobium silicides Nb_4Si, Nb_3Si, Nb_5Si_3, and $NbSi_2$ but also with the systems Nb_2O_5—SiO_2, Nb—Si—N, Nb—Si—B, and Nb—Si—C. A number of compounds that are of interest to the molecular chemist, though they have not yet been adequately investigated, are found in the niobium-phosphorus system, in which, besides the niobium phosphates, a series of compounds of $NbCl_5$ and $PCl_5([PCl_4][NbCl_6])$ or $OPCl_3$ and the niobium phosphorus nitride chlorides such as $NbNCl_2(PNCl_2)_{10}$ or $NbOCl_2(PNCl_2)_{10}$ are discussed. The volume ends with reports on the niobium-arsenic, niobium-antimony, and niobium-bismuth systems, which have not yet been studied very deeply.

The literature is fully covered up to 1968 in Volume B 1, and a number of important articles of later date are also mentioned.

Ekkehard Fluck [NB 968 IE]

Grundlagen der Organischen Chemie (Fundamentals of Organic Chemistry), by *H. R. Christen.* Verlag Sauerländer, Aarau, und Diesterweg-Salle, Frankfurt (Main) 1970. 1st Edit., 928 pp., numerous figures, bound DM 72.—.

The "Grundlagen der allgemeinen und anorganischen Chemie" (Fundamentals of General and Inorganic Chemistry) published by the same author in 1968 is now followed by the organic counterpart. A similar layout and arrangement has been used here. The subject matter is presented from the point of view of the reactions and the physicochemical principles, and the description of substances is deliberately avoided.

However, this layout is no longer as unconventional in a textbook of organic chemistry as the author suggests in

the foreword. Most of the modern textbooks in English in particular are arranged in this way. The layout of the present book is very similar *e.g.* to that of the excellent textbook by *D. I. Cram* and *G. S. Hammond*.

The present book is divided into three large parts:

1. Survey of the principal groups of organic substances.
2. Organic reactions.
3. A few special chapters on organic chemistry.

The first part contains an introduction, which is essentially a discussion of bonding states and of analysis. This is followed by a discussion of hydrocarbons, compounds with simple functional groups, and compounds with unsaturated functional groups.

The second part is divided into the chapters: General, Structure and Reactivity, Nucleophilic Substitutions on Saturated C Atoms, Elimination Reactions, Electrophilic Additions to C—C Multiple Bonds and Related Reactions, Other Additions to Double and Triple Bonds, Nucleophilic Substitutions on Unsaturated C Atoms, Nucleophilic Additions to Carbon-Hetero Multiple Bonds, Electrophilic Substitutions on Aliphatic C Atoms, Aromatic Substitution I: Electrophilic Substitution, Aromatic Substitution II: Nucleophilic Substitution, Free-Radical Reactions, Oxidations and Reductions and Rearrangements.

The third part contains the chapters: Heterocyclic Compounds, Lipids, Terpenes, Steroids, Carbohydrates, Proteins and Conjugated Proteins, Synthetic High Molecular Weight Substances, and Dyes.

A set of questions is appended to the subject matter of each chapter. The choice of examples and the presentation of the material with reference to physico-chemical aspects and reaction mechanisms are excellent. The formulas, figures, and tables are very clear and well selected. This textbook can be unreservedly recommended, and should play an important part in instruction at German universities in the near future.

However, I am of the opinion that a textbook of this type is suitable for the study of organic chemistry only if the student also has access to a book that concentrates on the material side. This is in fact recommended by the author in his foreword.

Hermann Stetter [NB 969 IE]

Free Nitroxyl Radicals. By *E.G. Rozantsev*, translated by *B. J. Hazzard*. Plenum Press, New York–London 1970. 1st Edit., xiv, 249 pp., $ 19.50.

Nitroxyl radicals, which are mainly derived from the 2,2,6,6-tetramethylpiperidine-1-oxyl type, are among the most interesting and most extensively studied radicals of organic chemistry because of their ready availability, their unusual stability (which enables them to undergo many chemical reactions without loss of their free-radical nature), and their very simple ESR spectra. Much of the existing knowledge of these radicals is due to the work of *E.G. Rozantsev*, who leads a section dealing with stable free radicals at the Moscow Academy of Sciences, and his colleagues. This is the source, not only of the main syntheses and transformations that proceed without loss of free-radical character, but also of many physical and biochemical studies concerned with the use of these radicals in a wide range of fields. Their importance has grown immensely in biochemistry during recent years, partly in connection with the concept of spin-labeling.

The translation of the book from the original Russian into English provides easier access to the results of these studies, which have appeared in numerous publications, mostly in Russian journals. It is regrettable that the more recent literature (published since 1968) is not covered, particularly in view of the extremely interesting developments that have taken place during this period. Moreover, the translation (surprisingly even in the short introductory chapter, which was not taken from the original) contains a series of outdated or incorrect structural formulas (*e.g.* pp. 2, 32, 48, 149) and some textual obscurities that could have been avoided by a more competent translator.

The book, which is intended mainly for the preparative chemist, requires no mathematical background and is easy to understand. It contains good illustrations of the ESR spectra, as well as all the important data on the chemistry and the physico-chemical properties of this group of radicals. The chapters on the di-, tri-, and tetraradicals, the mutual effects of the ESR spectra in connection with the conformation, and the review of the possible applications, which are becoming increasingly numerous, are particularly interesting. The book ends with a preparative section containing detailed instructions for the synthesis of various nitroxyl radicals.

Karl Dimroth [NB 972 IE]

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Generation of Carbenes by Thermal Cycloelimination

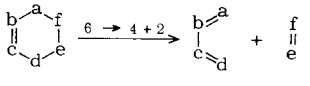
By Reinhard W. Hoffmann[*]

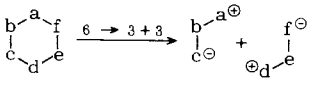
The growth of interest in carbenes has led to a need for methods that allow their generation in unimolecular decomposition processes, possible also in the gas phase, without troublesome by-products. Besides the decomposition of diazo compounds, thermal cycloeliminations from carbocycles and heterocycles with odd numbers of ring atoms have been found to be suitable for this purpose. The problems, structural requirements, and scope of such cycloelimination reactions are discussed in the present progress report. The advantages of carbene generation by thermal cycloelimination are demonstrated with reference to dialkoxycarbenes, which are very difficult to obtain in any other way.

1. Introduction

Cycloelimination is the cleavage of a carbocycle or heterocycle into two or more, usually independent fragments. Cycloelimination is thus defined as the reverse of a cycloaddition. It can be classified in the same way as the latter[1], and is also subject to the selection rules[2] imposed by the conservation of orbital symmetry.

Cycloeliminations from a ring having an even number of members can lead to fragments that all contain an even number of former ring atoms; the retro-Diels-Alder reaction serves as an example of a [6→4+2] cycloelimination. Since even fragments, such as $>C=C<$, $N\equiv N$, $>C=\underset{|}{C}-\underset{|}{C}=C<$, have saturated valences and are therefore of relatively low energy content, a [6→4+2] cycloelimination is normally favored over a [6→3+3] cycloelimination[3], which leads to odd fragments.





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Odd fragments generally[4] do not have their valences saturated and are therefore reactive intermediates such as 1,3-dipoles, carbenes, or nitrenes. Cycloelimination from rings with odd numbers of ring atoms must inevitably yield such odd fragments.

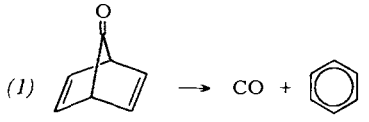
Cycloeliminations lead in a coupled reaction to two or more fragments[5]. If one of the fragments is a high-energy, reactive intermediate, thermal cycloelimination can still be achieved under relatively mild conditions provided that the other fragment is thermodynamically very stable, as in the case of molecular nitrogen or benzene. In cycloeliminations of this type, the exothermic formation of the stable fragment makes the endothermic formation of the reactive intermediate possible.

Cycloeliminations may be thermally or photochemically initiated, and do not require the presence of other reagents. It follows from this and from the reasons given earlier that cycloeliminations provide an ideal method of producing bifunctional reactive intermediates in the absence of interfering reactants. Hence, carbenes and 1,3-dipoles, as well as torsionally strained alkenes, angularly strained cycloalkynes, and dehydroaromatic compounds, can be generated, to study their intramolecular and intermolecular stabilization reactions.

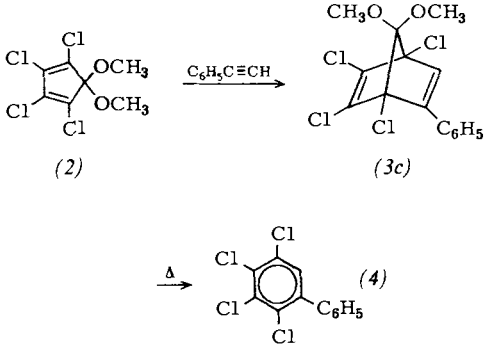
The present report summarizes what we have learned so far about the production of carbenes by thermal cycloeliminations, while the progress report that follows[6] presents a survey of photochemical cycloeliminations.

2. Cycloeliminations from Norbornadienes

The thermal [5→4+1] cycloelimination of carbon monoxide from norbornadienone *(1)* proceeds so readily that *(1)* has so far been intercepted only as a reactive intermediate[7],



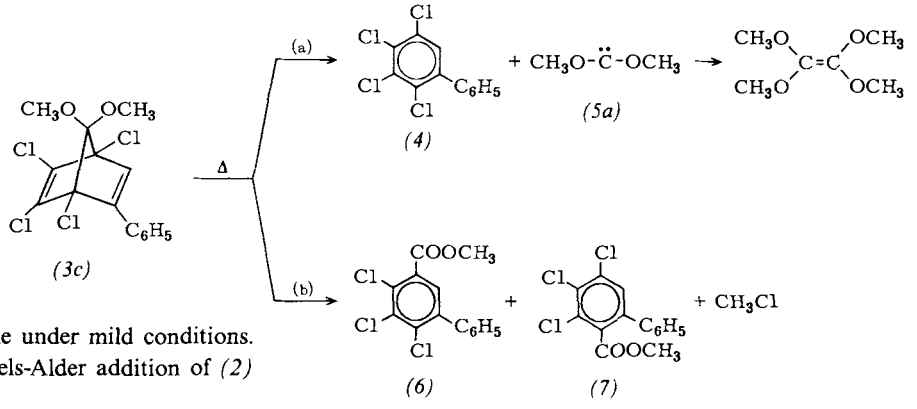
but has not been isolated[8]. The cycloelimination of carbenes, closely related to carbon monoxide in structure, should therefore also be possible under mild conditions. This is demonstrated by the Diels-Alder addition of *(2)*



to phenylacetylene, which led not to *(3c)* but to *(4)*[9]. Reinvestigation[10, 11] showed that *(3c)* can be isolated if the reaction is carried out under mild conditions. Only at 100—150 °C does the substance decompose with formation of *(4)* and [as a further reaction product of dimethoxycarbene *(5a)*] tetramethoxyethylene (see Scheme 1).

Cleavage of the bridge to give the esters *(6)* and *(7)* competes with this thermal cycloelimination of carbene *(5a)*.

β-Chloroalkyl esters are similarly formed on thermolysis of the cyclic acetals *(3j)*—*(3n)*. The competition of ring

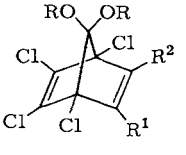


Scheme 1.

cleavage and cycloelimination is typical of the thermolysis of many 1,2,3,4-tetrachloro-7,7-dialkoxynorbornadienes, as shown in Table 1.

Closer investigation of the thermal decomposition of *(3c)* showed[11] that it is a first order reaction and that the rate of cycloelimination [path (a)] is practically independent of the polarity of the solvent ($k_{CH_3CN}/k_{cyclohexane} \approx 4$), whereas the ring cleavage [path (b)] is strongly favored by polar solvents ($k_{CH_3CN}/k_{cyclohexane} \approx 400$). The com-

Table 1. Product distribution on thermal decomposition of *(3)* (cf. Scheme 1).



(3)

	2 R	R^1	R^2	*T* (°C)	Yield (%) Path (a)	Path (b)	Ref.
a	$2\,CH_3$	H	H	85	38	50	[12]
b	$2\,CH_3$	H	Br	130	27	72	[10]
c	$2\,CH_3$	H	C_6H_5	100–150	see Table 2		
d	$2\,CH_3$	H	CH_3	160	84	—	[11]
e	$2\,CH_3$	CH_2OAc	CH_2OAc	140	60	?	[13, 14]
f	$2\,CH_3$	CH_2OAc	$CH(CH_3)OAc$	140	70	?	[13, 14]
g	$2\,CH_3$	$Sn(CH_3)_3$	$Sn(CH_3)_3$	140	40–60	?	[14, 15]
h	$2\,CH_3$	—CO—O—CO— [b]		190	[a]	[a]	[16]
i	$2\,C_6H_5CH_2$	H	C_6H_5	160–195	[a] 3:1	[a]	[11]
j	$-CH_2-CH_2-$	H	H	120	94	2	[12]
k	$-CH_2-CH_2-$	H	CH_3	160	100	—	[11]
l	$-CH_2-CH_2-$	H	C_6H_5	130–170	95	?	[11]
m	$-CH(CH_3)-CH(CH_3)-$	H	H	105	72	28	[12]
n	$-CH(CH_3)-CH(CH_3)-$	H	C_6H_5	140–150	80	10	[12]

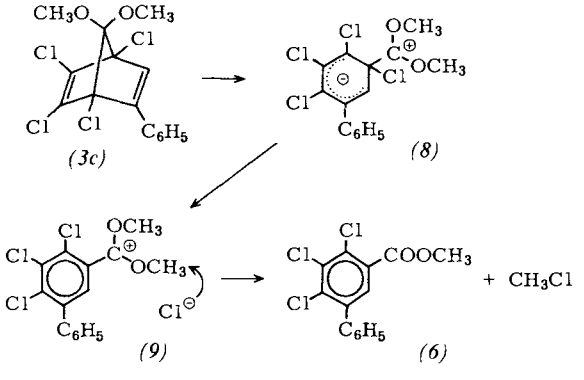
[a] Products of this reaction path were only detected qualitatively.
[b] The free dicarboxylic acid was used for the reaction.

petition between paths (a) and (b) can therefore be controlled by suitable choice of solvent (cf. Table 2), the cycloelimination predominating in apolar media.

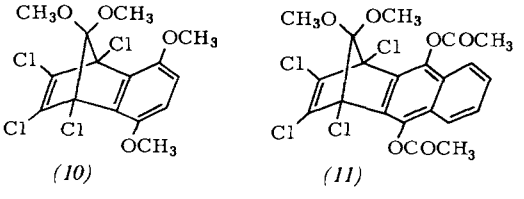
Table 2. Ratio of the reaction paths (a):(b) (cf. Scheme 1) in the thermolysis of *(3c)* as a function of the solvent [10, 11].

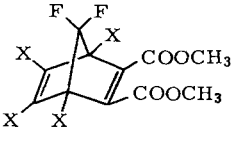
Solvent	115 °C (a):(b)	125–130 °C (a):(b)
Cyclohexane	12.6:1	
CCl_4		1.7:1
Pure		1.4:1
1,2-Dimethoxyethane	0.54:1	
CH_3OH	0.31:1	0.65:1
Pyridine		0.41:1
Acetonitrile	0.14:1	

Assuming that formation of *(6)* begins with rate-determining cleavage of *(3c)* to form the zwitterion *(8)*, it is understandable that the process is favored by polar solvents. *(8)* corresponds to the intermediate of a nucleophilic aromatic substitution, and should therefore readily lose chloride *via (9)* to give *(6)*[17]. In the pyrolysis of 1,2,3,4-tetrachloro-7,7-dimethoxynorbornadiene *(3a)* in ethanol, some ethyl 2,3,4-trichlorobenzoate, evidently formed from a cation analogous to *(9)*, was isolated. This product could not have been formed by transesterification of the initially formed methyl ester, since this reaction is too slow under the applied conditions[12].



The ring cleavage [path (b)] is favored not only by polar solvents but also by substituents on the ring that stabilize a negative charge. Thus path (b) is considerably more prominent in the thermolysis of *(3b)* than in that of *(3a)*. Finally, the reaction of *(2)* with esters of acetylenedicarboxylic acid leads [*via* the adduct *(3)*, $R^1 = R^2 = COOCH_3$] only to ring-opened products[18–20]. (Similar observations are reported in [21, 22].)

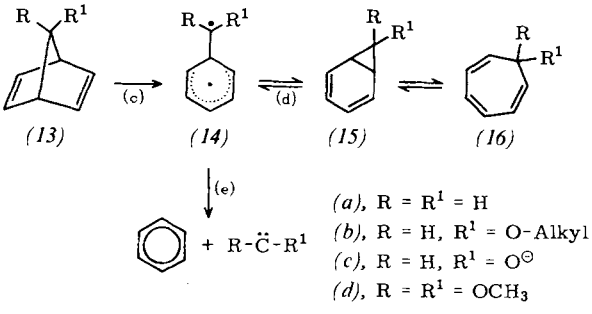




As expected, the cycloelimination of dimethoxycarbene *(5a)* becomes increasingly easy with increasing stability of the resulting aromatic compound. Thus the temperatures required for cycloelimination from *(10)* or *(11)* are about 100 °C higher than those required for cycloelimination from *(3a)*[10, 21], since with *(10)* or *(11)* the gain in aromatization energy is less than on formation of *(4)*. Similarly, difluorocarbene was liberated from *(12)* in good yields only at temperatures above 450 °C[23]. Thus it must be stabilized to a smaller degree than dimethoxycarbene *(5a)*.

2.1. Mechanism of the Cycloelimination

The cycloelimination of a carbene from a norbornadiene may proceed in one step as a symmetry-allowed cheletropic reaction. However, a non-concerted path is nevertheless possible. This becomes clear when one considers the cycloeliminations from *(3)* in the light of the thermal behavior of other norbornadiene derivatives (see Scheme 2).



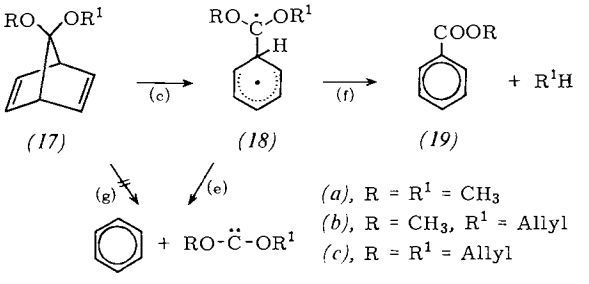
Scheme 2.

Thus norbornadiene *(13a)* isomerizes when heated to give cycloheptatriene *(16a)*[24]. Similar reactions are found for 7-alkoxynorbornadienes *(13b)* and 7-phenylnorbornadiene[25], as well as for norbornadien-7-olate *(13c)*[25a]. The isomerization *(13)*→*(16)* has been formulated as proceeding *via (14)* and *(15)*[25,26]. A comparison of the temperatures required for the rearrangement, *i.e.* 450 °C for *(13a)*, 270 °C for bornadiene[27], 170 °C for *(13b)*[25], and 25 °C for *(13c)*[25a], showed that the rate-determining step *(13)*→*(14)* is facilitated by radical-stabilizing substituents on C-7. *(13d)* should therefore isomerize particularly readily; in this case, however, cycloelimination of dimethoxycarbene *(5a)* was observed on heating at 150 °C[28]. From the above, it is therefore deduced that the same step (c) is involved and is rate-determining in the cycloelimination as well as in the isomerization. This readily explains why the cycloelimination of *(5a)* from *(3a)* proceeds at a temperature about 70 °C lower than that required in the case of *(13d)*, since the four chlorine substituents in *(3a)* should considerably facilitate the formation of the intermediate *(14)*.

According to this view, it is not at the stage *(13)* but at *(14)* that the reaction path branches to give either cycloelimination or isomerization to *(16)*. Since the ring closure of *(14)* to form norcaradiene *(15)* [path (d)] should be exothermic, the cleavage of *(14)* [path (e)]

can compete with path (d) only if it also is exothermic [unless the temperatures chosen are so high that the equilibrium between *(14)* and *(16)* is established (cf. Section 3)]. Of course, exothermicity is conveyed to path (e) not only by the stability of the aromatic fragment formed but also by that of the carbene.

Evidence indicating that the cycloelimination of dialkoxycarbene from *(13d)* proceeds *via (14)* as an intermediate can be obtained from intramolecular competition experiments in which an additional partitioning of the reaction at *(14)* is introduced (Scheme 3). The intermediate *(18a)*≡*(14d)* can thus in principle undergo an irreversible free-radical elimination to form *(19a)* [path (f)], but this is only of minor importance compared to cycloelimination in the gas-phase pyrolysis of *(17a)*[28–30].

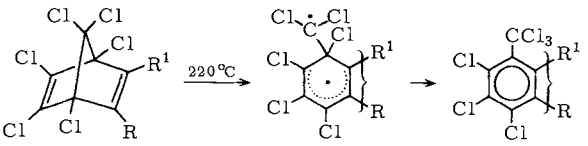


Scheme 3.

Elimination of a radical R or R^1 from a dialkoxyalkyl radical such as *(18)* should become more facile with increasing radical stability of R or R^1[31]. Thus in the pyrolysis of *(17b)*, the formation of *(19b)* and the cycloelimination of the carbene were equally fast[29,32], whereas in the case of *(17c)* the formation of *(19c)* predominated over the cycloelimination. Elimination of the allyl radical thus proceeds at the expense of carbene formation. This is in accordance with Scheme 3[33], provided the rate of step (e) does not vary much for the substrates *(18a)*—*(18c)*.

Finally, other irreversible reactions starting with *(14)* can completely suppress cycloelimination, as occurs when *(20)* is heated above 220°C[11,34]. In this case rearrangement *via (21)* to *(22)*, without elimination of dichlorocarbene, is observed.

The hypothesis that the cycloelimination of dimethoxycarbene *(5a)* from *(13d)* proceeds *via (14d)* can also be confirmed by other experiments, since the steps between *(14)* and *(16)* in Scheme 2 are very probably reversible, as has been shown for a derivative with $R=R^1=CH_3$[35]. *(14d)* should thus be accessible independently by heating



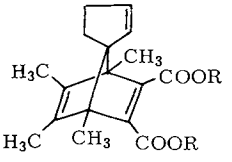
(20) *(21)* *(22)*

R	R^1
$ClCH_2$	$ClCH_2$
H	$ClCH_2$
H	CH_2OCOCH_3
H	$COOC_2H_5$
H	C_6H_5
$COOCH_3$	$COOCH_3$

(16d), a process that should give the same products as the thermolysis of *(13d)*. *(16d)* does in fact decompose into dimethoxycarbene and up to 54% of benzene at 130 to 350°C[36,37].

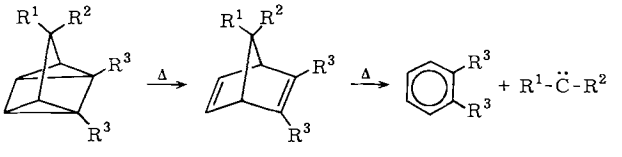
The pyrolysis of *(16d)* also leads to products[38] that are not formed on thermolysis of *(13d)*. *(16d)* cannot therefore be an intermediate in the pyrolysis of *(13d)*, as was once suggested[25].

It is quite possible, however, that the equilibrium between the compounds of the types *(14)* and *(16)* is established in the cycloelimination of an unstabilized carbene, *e.g.* of 2-cyclopenten-1-ylidene from *(23)* at 350°C[39].



(23)

Quadricyclane derivatives *(24)* can also be used for cycloeliminations of this type. As can be seen from Table 3, this requires higher temperatures, and it can therefore be assumed that *(24)* does not decompose directly to products but undergoes fast cycloelimination only after symmetry-forbidden isomerization to *(25)*. *(25e)* has in fact been isolated upon careful pyrolysis of *(24e)*[40].



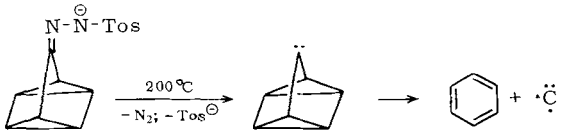
(24) *(25)* *(26)*

Table 3. Cycloeliminations from quadricyclane derivatives *(24)*.

	Substrate *(24)*				*(26)*		
	R^1	R^2	R^3	*T* (°C)	yield (%)	further products	ref.
(a)	OCH_3	OCH_3	$COOCH_3$	200	[a]	$(CH_3O)_2C=C(OCH_3)_2$	[41]
(b)	$-O-CH_2-CH_2-O-$		$COOCH_3$	125	100	CO_2, $CH_2=CH_2$	[41a]
(c)	$-O-CH_2-CH_2-O-$		H	200	95	CO_2, $CH_2=CH_2$	[28]
(d)	$-S-CH_2-CH_2-S-$		H	200	75	CS_2	[28]
(e)	$-O-C(CH_3)_2-$		$COOCH_3$	260	60	$(CH_3)_2C=C=O$	[40]

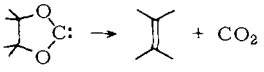
[a] Detected qualitatively.

A carbene functionality at the one-carbon bridge of norbornadiene (or quadricyclane) is sufficiently rich in energy to allow the elimination of the bridge as atomic carbon[41b].



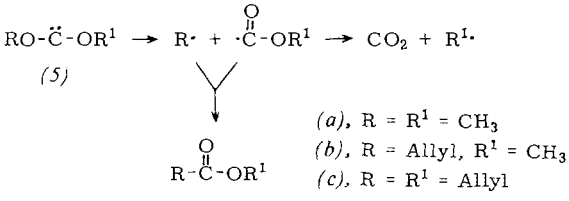
2.2. The Carbenes Liberated

In most of the examples investigated so far, a dialkoxycarbene was liberated by cycloelimination from a 7,7-disubstituted norbornadiene. If the cycloelimination leads to a 1,3-dioxolan-2-ylidene (2-carbena-1,3-dioxolane) *(27)*, this immediately undergoes further cycloelimination[42] to give carbon dioxide and an olefin[11,12,28,41a].



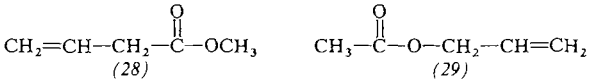
(27)

In the case of dimethoxycarbene *(5a)*, the nature of the further reaction products is strongly dependent on the manner in which the cycloelimination is carried out. If *(3c)* is pyrolyzed rapidly in the condensed phase, corresponding to a high stationary concentration of *(5a)*, the carbene is almost completely dimerized to tetramethoxyethylene[10,11]. If on the other hand *(3c)* is pyrolyzed at a high dilution in the gas phase, *(5a)* isomerizes to form methyl acetate[10,11,28,43]. This rearrangement probably proceeds *via* free radicals in which formation of methyl acetate competes with further fragmentation into carbon



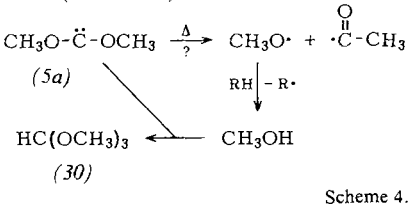
dioxide and ethane[28]. This fragmentation is favored by residues R that form stable free radicals. Thus the fragmentation of *(5b)* predominates over the rearrangement at 240 °C, and *(5c)* gives only carbon dioxide and biallyl[32].

In the rearrangement of *(5b)*, the migration of the allyl residue to give *(28)* competes with that of the methyl group to give *(29)*. The allyl residue migrates only about



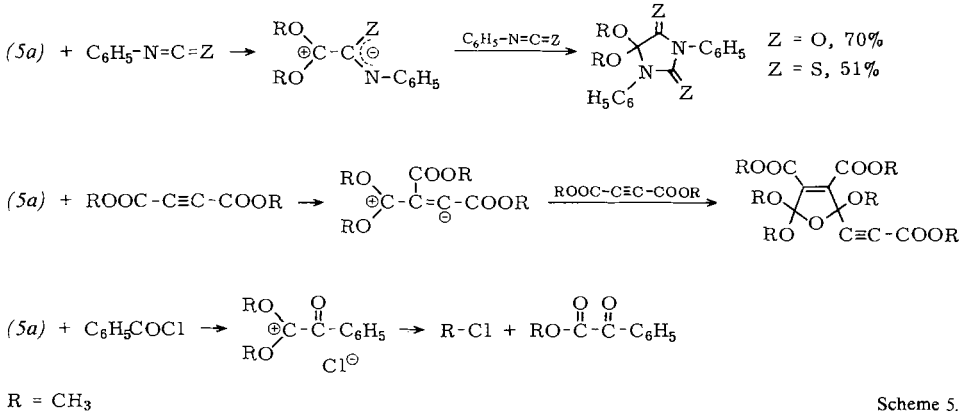
twice as rapidly as the methyl, indicating that free-radical character is not yet very pronounced in the transition state, *i.e.* that the transition state of the rearrangement occurs early on the reaction coordinate. Moreover, deuterium labeling suggested that in the migration of the allyl residue, the allyl moiety separates completely from the remainder of the molecule, as is necessary for a free-radical rearrangement. Thus an equally conceivable [2,3]-sigmatropic process was not observed at the high temperature of 240 °C[32].

It is not yet certain whether dialkoxycarbenes undergo a different type of thermal decomposition into alkoxyl and acyl radicals in the condensed phase[44,45]. In any case, 60—70% of methyl orthoformate *(30)* is formed on pyrolysis of *(3c)* or *(13d)* in the presence of hydrogen donors[11,28]. The formation of this ester could proceed as shown in Scheme 4. The propensity of *(5a)* to add methanol is confirmed independently by the fact that *(5a)* can be intercepted in good yields as *(30)* in the pyrolysis of *(3c)* in methanol[10] (cf. also[36]).



Scheme 4.

Dialkoxycarbenes have also been intercepted in many other reactions that leave no doubt as to their formation in the cycloelimination from 7,7-dialkoxynorbornadienes. Thus the pyrolysis of *(3c)* in the presence of air gave dimethyl carbonate as an autoxidation product of *(5a)*[10,11], while *O,O*-dimethyl thiocarbonate was formed in the presence of sulfur[10]. A [1+2] cycloaddition of *(5a)* to electrophilic olefins has not yet been achieved[11,46], but as one would expect from its nucleophilic character, *(5a)* adds to electrophilic multiple bond systems to form 1,3-dipoles[47], the further reaction products of which have been isolated[46] (Scheme 5). The carbene *(5a)* has been acylated in a similar manner.

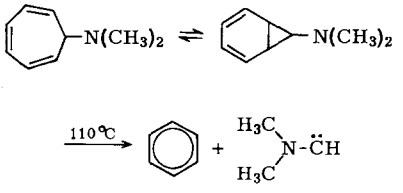


Scheme 5.

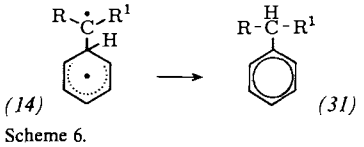
The cycloelimination from norbornadiene derivatives can be used not only for the liberation of dialkoxycarbenes, but also for the production of $(CH_3)_2Si$[48], $(C_6H_5)_2Si$[49], and $(CH_3)_2Ge$[50], as well as of C_6H_5P[51] and C_6H_5As[52], the stabilization reactions of which have not yet been investigated.

3. Cycloelimination from Norcaradienes

The thermal cleavage of 7,7-dimethoxycycloheptatriene *(16d)* into dimethoxycarbene *(5a)* and benzene (Section 2.1) was interpreted as a cycloelimination from a 7,7-dimethoxynorcaradiene *(15d)*. Cycloeliminations that probably proceed *via* norcaradienes can also be achieved from other cycloheptatriene derivatives. Thus dimethylaminocarbene is eliminated, though only in a yield of about 5%, from 7-dimethylaminocycloheptatriene at 110 °C[53,54].



A temperature of 470 °C is required for the cycloelimination of unsubstituted methylene from cycloheptatriene[55]. These [3→2+1] cycloeliminations are a reversal of the well-known [1+2] cycloaddition of carbenes to aromatic compounds[56]. When heated, cycloheptatrienes normally isomerize *via* norcaradienes and biradicals of the type *(14)* to form derivatives of toluene[35]. At the reaction temperature, which is usually higher than in the pyrolysis of norbornadienes, the intermediate *(14)* is stabilized by migration of a hydrogen atom to form *(31)*.



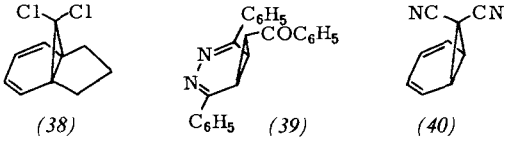
Scheme 6.

Cycloelimination of carbenes from norcaradienes can therefore be expected only if the carbene formed is sufficiently stabilized or if the hydrogen shift is not possible on structural grounds. The latter situation is found in the following examples.

When *(32)* is heated at 250 °C the intermediate *(34)* is formed *via* the norcaradiene *(33)* and eliminates methylene[57].

The intermediate *(36a)* that occurs in the thermolysis of 1,6-methano[10]annulene *(35a)*, on the other hand, does not liberate methylene but isomerizes to form *(37a)*[58]. Only when the carbene to be eliminated is also stabilized, as in the cases of *(35b)* and *(35c)*, is cycloelimination of the dihalocarbene observed in yields of more than 90% at 250 and 60 °C respectively[58, 59].

If the norcaradienes that are present only in equilibrium with cycloheptatrienes undergo thermal [3→2+1] cycloeliminations, the same should also be expected of norcaradienes that are present entirely as such. This is in fact so for *(38)*, which yields dichlorocarbene at 150 °C[58, 59], and for *(39)*, which loses benzoylcarbene at 195 °C[60].

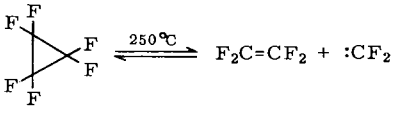


On the other hand, no dicyanocarbene is lost from norcaradiene *(40)* since isomerization to phenylmalononitrile (Scheme 6) occurs very readily[61]. However, cycloelimination, even of energy-rich carbenes, from norcaradienes can be achieved photochemically in medium to good yields[6, 60–62].

4. Cycloeliminations from Cyclopropanes

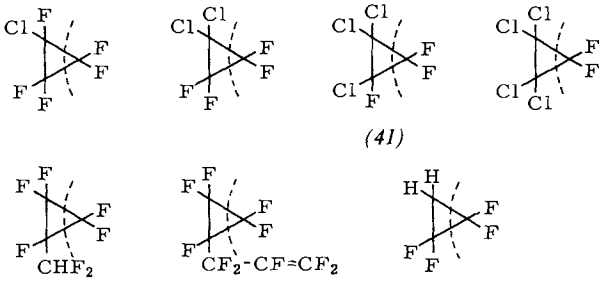
In a cycloelimination from a monocyclic system the gain in stabilization energy in the even fragment can no longer be as great as in the examples in the last section. It is therefore to be expected that [3→2+1] cycloeliminations of this type can be achieved thermally only if the carbenes liberated are stabilized and particularly low in energy.

Authentic[63] thermal cycloeliminations of carbenes are in fact known only for fluorinated cyclopropane derivatives, the deciding factor in this case probably being the low energy of difluorocarbene. Thus hexafluorocyclopropane liberates difluorocarbene in a yield of more than 85% at 250 °C[64, 65], and the carbene dimerizes to tetrafluoroethylene if it is not intercepted by cycloaddition to other olefins.



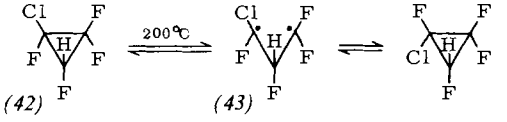
A cyclopropane ring can in principle be broken in three ways. Thus dichlorocarbene, chlorofluorocarbene, and difluorocarbene could be liberated from *(41)*. As is shown

by the following examples[65–67], only the most stable carbene, difluorocarbene, is liberated in such cycloeliminations at 160—270 °C.



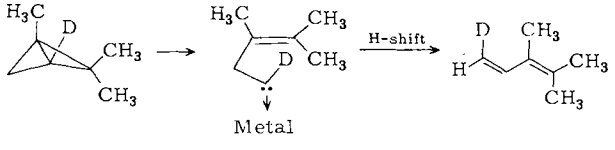
(41)

The structurally similar compound *(42)* undergoes a clean *cis-trans* isomerization in the same temperature range[68] which is best explained by cleavage to form the biradical *(43)*. Therefore the cycloeliminations from the other perhalogenated cyclopropanes probably proceed nonconcertedly *via* an intermediate corresponding to *(43)*.



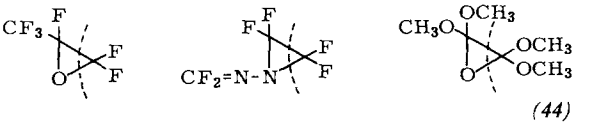
(42) *(43)*

Strained cyclopropane ring systems such as bicyclo[1.1.0]-butane derivatives undergo rearrangements when treated with $[Rh(CO)_2Cl]_2$, $[C_6F_5Cu]_4$, Cu_2Cl_2, or $HgBr_2$ at temperatures as low as 0—50 °C. This rearrangement is most readily accounted for in terms of a [3→2+1] cycloelimination to form a carbene-metal complex[68a]. Undoubtedly this process is considerably facilitated by the ring strain in the starting materials.



5. Cycloeliminations from Three-Membered Heterocycles

The thermal [3→2+1] cycloelimination is not confined to perhalogenated cyclopropanes. Perhalogenated oxiranes and aziridines also generate the most stable possible carbene, and do not split off the hetero atom, as is shown by the following examples[68–70].

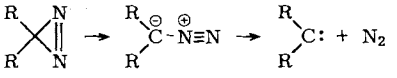


(44)

(44), which is formed only as an intermediate, probably decomposes similarly into *(5a)* and dimethyl carbonate[71].

In the case of the oxiranes and aziridines, the cycloelimination may be preceded by electrocyclic ring opening to give a 1,3-dipole[72]. Whereas this has been verified for the photochemical cycloelimination of carbenes from oxiranes [6, 73], the question has not yet been answered for the thermal reactions described above.

The cycloelimination of a carbene from diazirines is particularly favored by the low energy of molecular nitrogen. Diazirines readily yield carbenes both thermally and photochemically; a preceding electrocyclic ring cleavage to give a diazoalkane has been detected at least in the latter case[74, 75].



Since the cycloeliminations from diazirines have already been reviewed[74, 76], we shall merely mention here that these reactions are the only established route to mixed hetero-substituted carbenes such as $CH_3O—\ddot{C}—F$ and $NC—\ddot{C}—F$[77] (and potentially also $CH_3O—\ddot{C}—Cl$, $CH_2=CH—\ddot{C}—Cl$, or even $CH_3—\ddot{C}—O—COCH_3$[78]), and that they allow the study of the interaction of carbenes with strong acids such as trifluoromethanesulfonic acid[79] or with oxidizing agents such as Cl_2, N_2O_4, or NO_2Cl[80].

6. General Considerations

In retrospect, it can be seen that thermal cycloeliminations allow the liberation of stabilized carbenes, but not of reactive carbenes such as methylene. The fact that it is possible in this way to liberate dialkoxycarbenes whose generation by other routes[81] is unsatisfactory, or to produce difluorocarbene under mild conditions and in the gas phase, is not the real incitement of these investigations. Instead the reason lies in the mechanistic aspects of these reactions.

The cycloeliminations of carbenes discussed here have already been considered theoretically as cheletropic reactions[2]. For all processes of this type an orbital symmetry-allowed path is available, the "choreography" of which prescribes a linear movement of the groups for the [5→4+1] cycloelimination and a nonlinear movement for the [3→2+1] cycloelimination. These hypotheses cannot yet be verified, owing to lack of stereochemical criteria.

The data discussed in Sections 3 and 4 point to a two-step course for the [3→2+1] cycloelimination, and are thus clearly different from the addition of carbenes to olefins, which proceeds in one step and nonlinearly[82]. However, it has already been pointed out in a similar connection that the cycloaddition and its reversal, *i.e.* the cycloelimination, need not follow the same reaction path[83].

Many more data are available on linear cheletropic [5→4+1] cycloeliminations, which are generally one-step processes[2] if stereochemistry is used as the criterion. It is therefore the more surprising that the symmetry-allowed [5→4+1] cycloelimination of dialkoxycarbenes *(5)* from 7,7-dialkoxynorbornadienes *(17)* very probably proceeds in several steps as shown by the data in Section 2. Since most known electrocyclic reactions strictly follow the orbital symmetry rules, it is particularly interesting to

search for the reasons why some deviate from the allowed and hence normally energy-favored path.

It may be characteristic of the present system that the reversal, *i.e.* the symmetry-allowed [4+1→5] cycloaddition of a carbene to an aromatic compound, is unknown. The reactions of carbenes with aromatic compounds have always been found instead to result in [2+1→3] cycloaddition to give norcaradiene derivatives[56]. Perhaps the energy surface of the norbornadienes permits a symmetry-allowed, low-energy transition into the energy surface of the norcaradienes[27], from which, apart from a nonlinear cheletropic elimination, only a stepwise cycloelimination is possible.

The thermal behavior of the norbornadienes and norcaradienes could however simply be due to the fact that two carbon-carbon bonds must be broken simultaneously in a synchronous cycloelimination, whereas the cleavage of only one bond requires less energy and leads directly to a stabilized intermediate *(14)*.

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Generation of Carbenes by Photochemical Cycloelimination

By Gary W. Griffin[*]

A wide variety of shelf stable substrates undergo photochemical cycloelimination under relatively mild conditions. Suitable substrates include cyclopropanes, oxiranes, aziridines, and diazirines, as well as 3H-pyrazoles and 1,3-dioxolanes. Carbenes prepared from these substrates as well as certain cyclic carbonates, sulfites, and phosphoranes behave chemically in a manner similar to divalent carbon species produced from conventional diazo precursors, namely, they react with alkenes to give cyclopropanes and undergo insertion into C—H bonds of alkanes. In many cases the carbenes formed may also be detected by EPR and optical spectroscopic methods.

1. Introduction

It has become increasingly apparent that divalent carbon intermediates play an important role in the photochemistry of a variety of organic substrates. In many cases the reactions have synthetic utility which may complement conventional techniques for the generation of carbenes. It is our intent in this review to summarize those examples of photoinduced cycloeliminations which lead to carbene formation. In accordance with the precedent established in the related review[1a] on thermolytic cycloeliminations we shall employ the convention suggested by *Huisgen*[1b] in designating the mode of cycloelimination.

To the extent that the reactions described herein are concerted they are subject to orbital symmetry constraints[1c]. For example the [3→2+1] cycloelimination reaction of a cyclopropane to give a carbene if entirely

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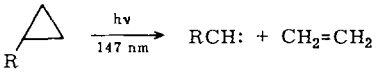
concerted has been classified as a cheletropic reaction (*i.e.*, a reaction in which two sigma bonds terminating at a single atom are broken in concert) and the orbital symmetry theory and selection rules for such processes have already been advanced[1c, 1d].

When intermediates are implicated in the cycloeliminations reviewed constraints are still imposed on the bond breaking process leading to the intermediate(s) which affects the stereochemical mode of ring opening[1c, 1d]. Where in the author's opinion the data available merit discussion of such theoretical considerations they are included for the reader's benefit.

2. [3→2+1] Cycloeliminations

2.1. Carbenes from Cyclopropanes

An efficient method of synthesizing cyclopropanes involves cycloaddition of carbenes to alkenes. The [3→2+1] cycloelimination is the reverse of this well-known reaction, *i.e.*, the production of a carbene and an alkene by fragmentation of a cyclopropane. The parent hydrocarbon *(1a)* has been photolyzed in the vapor phase and gives methylene *(2a)* and ethylene[2] while photolysis of benzylcyclopropane



(1) *(2)*

(a), R = H
(b), R = $CH_2C_6H_5$

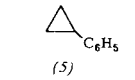
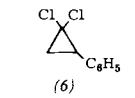
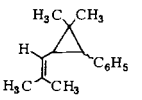
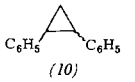
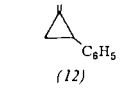
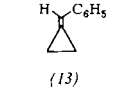
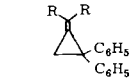
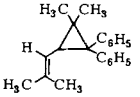
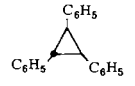
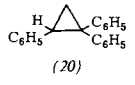
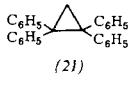
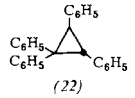
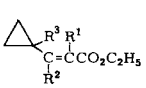
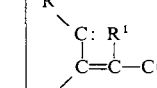
(1b) leads to extensive fragmentation to produce a number of hydrocarbons including ethylene and benylcarbene *(2b)*[3].

Aryl substitution of the cyclopropane ring should be accompanied by concomitant C—C bond weakening and more facile homolytic cleavage. The *cis-trans* thermo- and photoisomerization of aryl and aroyl substituted cyclopropanes reflect decreased bond strength[4]. Several reports of photolytic cycloeliminations involving aryl cyclopropanes are listed in Table 1.

Irradiation of phenylcyclopropane *(5)* in cyclohexene gives rise to methylene addition products, namely the isomeric methylcyclohexenes and norcarane. Methylene *(2a)* generated from *(5)* in hydrocarbon solutions exhibits the same indiscriminate insertion into aliphatic carbon-hydrogen bonds as does methylene generated from diazomethane or ketene[6a]. [3→2+1] Cycloelimination upon photolysis of *(5)* in the vapor phase is postulated to explain the formation of methylene as a primary product[6b]. Competitive photolytic reactions complicate the cycloelimination reaction with alkyl substituted phenylcyclopropanes[7].

1,1-Dichloro-2-phenylcyclopropane *(6)* undergoes photochemical cycloelimination to give primarily dichlorocarbene *(7)*[8]. The addition of *(7)* to olefins appears to occur in a *cis* fashion in a manner similar to that observed for other halocarbenes or carbenoids[9]. The isomeric phenylvinylcyclopropanes *(8)* are photolabile and when

Table 1. Examples of photocycloeliminations from cyclopropane derivatives.

Cyclopropane	Carbene	Yield (%)	Ref.
 *(3)*	$:CH_2$ *(2a)* $[H_2C{=}C{:}]$ *(4)*	not reported	[5]
 *(5)*	$:CH_2$ *(2a)*	not reported	[6]
 *(6)*	Cl_2C: *(7)*	9–15 [a]	[8]
 *(8)*	$(CH_3)_2C{=}CH\ddot{C}H$ *(9)*	≈10	[10]
 *(10)*	$C_6H_5\ddot{C}H$ *(11)*	7–8 [b]	[11, 12]
 *(12)*	$[H_2C{=}C{:}]$ *(4)*	≈33	[16]
 *(13)*	$[C_6H_5CH{=}C{:}]$ *(14)*	≈4	[16]
 *(15a)*, R = H *(15b)*, R = CH_3	$[H_2C{=}C{:}]$ *(4)* $[(CH_3)_2C{=}C{:}]$ *(16)*	≈0.5 3 [a]	[16] [17]
 *(17)*	$(CH_3)_2C{=}CH\ddot{C}H$ *(9)* $(C_6H_5)_2C$: *(18)*	45 38 [c]	[18]
 *(19)*	$C_6H_5\ddot{C}H$ *(11)*	5 [b]	[11, 19]
 *(20)*	$C_6H_5\ddot{C}H$ *(11)* $(C_6H_5)_2C$: *(18)*	trace [c] 7–10 [c]	[19]
 *(21)*	$(C_6H_5)_2C$: *(18)*	50	[19]
 *(22)*	$C_6H_5\ddot{C}H$ *(11)* $(C_6H_5)_2C$: *(18)*	not detected [c] 40	[19]
 *(23)*	 *(24)*	not reported	[20]

[a] Based on addition to alkenes to give cyclopropanes.
[b] As determined by the extent of insertion in alkanes and/or methanol.
[c] From extent of ether formation in alcohols.

irradiated give the vinylcarbene *(9)* and 2-methyl-1-phenylpropene among other rearrangement products[10].

cis- and *trans*-1,2-Diphenylcyclopropanes *(10)* undergo photointerconversion[4a] and the kinetics have been studied. Geometrical isomerization predominates by a ratio of 4:1 over branching to side products, which prevents attainment of a "true" photostationary state[12]. Upon prolonged irradiation of *(10)* in *n*-pentane (24—48 h) it is possible to achieve fragmentation to the extent of 7—8%[11]. The selectivity factor for secondary *versus* primary C—H insertion for phenylcarbene generated from *(10)* is 8.3 and essentially the same as that observed when conventional phenylcarbene precursors are used[13]. A trimethylene diradical accounts for the geometrical (as well as accompanying structural) isomerization[4a, 4c, 12].

A comprehensive study of the absorption and emission spectroscopy and photochemistry of six phenyl-substituted cyclopropanes has recently been carried out at 77 °K[14]. Long wavelength phosphorescences (maxima $\approx$575 nm, $\tau \approx 7$ ms) are observable for the diphenylcyclopropanes *(10)* as well as for the tri- and tetraphenylcyclopropanes studied. It is suggested that these phosphorescences arise from diradicals of the trimethylene type formed by photocleavage of the cyclopropane ring, presumably in the allowed disrotatory manner[15]. It is proposed that arylcarbenes in general and phenylcarbene in particular arise in turn by subsequent thermal homolysis of trimethylene diradicals. Possibly bond breaking may lead to a singlet diradical, potentially zwitterionic in character, since the sites of charge and spin presumably may be sufficiently close to accommodate orbital overlap. This problem has recently been faced experimentally by *Yankee* and *Cram*[4f] for thermal transformations of certain cyclopropyl systems.

Methylenecarbenes may be generated photolytically from methylenecyclopropanes. For example, irradiation of *(3)*, *(12)*, *(13)*, and *(15)* results in extrusion of methylenecarbenes *(4)*, *(4)*, *(14)*, and *(16)*, respectively, which with the exception of *(16)* rearrange to acetylenes faster than they can be trapped by solvent[5, 16, 17].

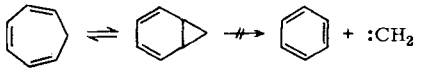
Zimmermann and *Pratt*[18] note that 1,1-dimethyl-2,2-diphenyl-3-(2-methylpropenyl)cyclopropane *(17)* undergoes two types of cycloelimination in *tert*-butanol. Upon photolysis, 1,1-diphenyl-2-methylpropene and presumably the vinylcarbene *(9)* are formed. Diphenylcarbene *(18)*, which is also produced, reacts with the solvent to give benzhydryl *tert*-butyl ether (38%).

A trend is discernable from the photochemical studies performed on the tri- and tetraphenylcyclopropanes *(19)* through *(22)*. It is apparent from data presented in Table 1 that when two options for cycloelimination exist, namely, formation of phenyl- and diphenylcarbene, then fragmentation to the latter predominates[19]. While no direct spectroscopic evidence for the formation of carbenes from the cyclopropanes *(19)* through *(22)* has yet been obtained, the chemical evidence for formation of these species is convincing. As with *(10)* determination of the relative insertion selectivity of phenylcarbene derived from *(19)* compares favorably with the values obtained using phenyldiazomethane[11, 13]. The formation of diphenylcarbene from *(20)*, *(21)*, and *(22)* is adduced from the behavior observed upon photolysis of these substrates in alkenes and/or methanol[19].

The photochemical response of six α,β-unsaturated esters of the type *(23)* to ultraviolet radiation has been studied by *Jorgenson*[20], who found fragmentation to carbenes *(24)* to be a surprisingly general mode of reaction for such cyclopropylacrylic esters.

2.2. Carbenes from Fused-Ring Cyclopropane Derivatives

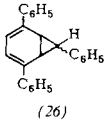
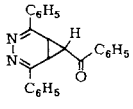
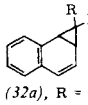
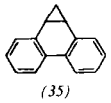
Examination of the products obtained on photolysis of cycloheptatriene *(25)* shows that under the conditions employed cycloelimination to methylene does not occur although a substantial driving force might be anticipated for fragmentation of norcaradiene[6b, 21].



(25)

The photolysis of 2,5,7-triphenylnorcaradiene *(26)* in ether (Table 2) affords *p*-terphenyl (4%). *Toda* and coworkers[22] propose that phenylcarbene *(11)* is formed on the basis of analogous reactions of other stable norcaradienes *(vide infra)* although trapping experiments were not successful. Fragmentation of 7-benzoyl-2,5-diphenyl-

Table 2. Examples of photocycloeliminations from compounds containing fused cyclopropane rings.

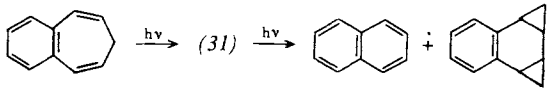
Precursor	Carbene	Yield (%)	Ref.
 *(26)*	$C_6H_5\ddot{C}H$ *(11)*	not reported	[22]
 *(27)*	$[C_6H_5C\ddot{O}\ddot{C}H]$ *(28)*	not reported	[23]
 *(29)*	$:C(CN)_2$ *(30)*	60	[24]
 *(31)*	$:CH_2$ *(2a)*	not reported	[25]
 *(32a)*, R = R¹ = CN *(32b)*, R = H; R¹ = $CO_2C_2H_5$ *(32c)*, R = H; R¹ = CO_2CH_3	$:C(CN)_2$ *(30)* $:CHCO_2C_2H_5$ *(33)* $:CHCO_2CH_3$ *(34)*	22 [a] 8 [a] 10 [a]	[24] [24] [26]
 *(35)*	$:CH_2$ *(2a)*	>90 [a]	

[a] As determined by the extent of insertion in alkanes and/or methanol.

3,4-diazanorcaradiene *(27)* to 3,6-diphenylpyridazine occurs and it is reasonable to assume that a carbene such as *(28)* may be formed as a transient product[23].

Photolysis of a cyclohexane solution of 7,7-dicyanonorcaradiene *(29)* gave cyclohexylmalononitrile[24]. Furthermore, the yields of insertion products obtained from *(29)* using 2,3-dimethylbutane as a solvent substrate (27% each of primary and tertiary C—H insertion product) were higher than those obtained when dicyanodiazomethane was employed as a precursor for dicyanocarbene *(30)* (12 and 16%, respectively). The similar product ratios observed upon photolysis of *(29)* and thermolysis of dicyanodiazomethane in 2,3-dimethylbutane are cited as evidence that the species formed from these independent sources have essentially the same relative reactivity toward primary and tertiary C—H bonds[24].

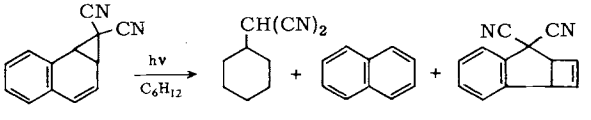
Pomerantz and *Gruber* examined the photochemistry of 7*H*-benzocycloheptene *(36)*[25]. Irradiation of dilute solutions of *(36)* in ether leads to benzonorcaradiene *(31)*



(36) *(37)*

(70—80%), which upon prolonged irradiation affords naphthalene and *(37)*. The hypothesis that methylene *(2a)* is transferred in the conversion of *(31)* into *(37)* and naphthalene was substantiated by trapping experiments utilizing cyclohexene.

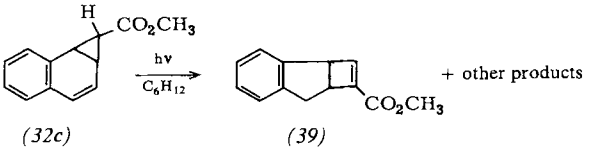
The photolysis of dicyanobenzonorcaradiene *(32a)* in cyclohexane has been studied by *Ciganek*[24] under conditions similar to those employed with *(29)*; cyclohexylmalononitrile (22%) in addition to naphthalene (22%) and a photoisomer of *(32a)* assigned structure *(38)* (44%) are formed. Irradiation of ethoxycarbonylbenzonorcaradiene *(32b)* in cyclohexane reportedly gives only a small amount



(32a) *(38)*

of the carbene transfer product ethyl cyclohexylacetate (8%), in addition to naphthalene (11%) and intractable material.

Inexplicably, a more complex spectrum of products was observed by *Swenton* and *Krubsack*[26] upon photolysis of methoxycarbonylbenzonorcaradiene *(32c)*. The products include naphthalene (13%), the insertion product methyl cyclohexylacetate (10%), methyl 1- and 2-naphthylacetate [(14%) and (5%), respectively] and *(39)* (11%).



(32c) *(39)*

In one of the earliest photocycloelimination studies dibenzonorcaradiene *(35)* was recommended as a stable, high yield (>90%) source of active methylene for small scale synthesis and ^{14}C labeling[6b]. The C—H insertion selectivity of methylene *(2a)* thus obtained compares favorably with the indiscriminate reactivity reported for methylene generated from diazomethane. The stereochemical mode of addition of methylene formed from *(35)* was examined by irradiation of this precursor in *cis*- and *trans*-4-methyl-2-pentene. In each case the products are identical to those obtained utilizing diazomethane.

2.3. Carbenes from Oxiranes

vic-Diaryloxiranes have been shown to undergo cycloelimination on photolysis in solution to give arylcarbenes and carbonyl compounds. This mode of reaction has been studied extensively and shown to possess broad synthetic utility. The results of these investigations are summarized in Table 3.

trans-Stilbene oxide *(40)* has been irradiated in methanol and alkenes[27, 28]. Under these conditions phenylcarbene *(11)* is trapped as benzyl methyl ether and the appropriate cyclopropane, respectively. According to expectations two epimeric cyclopropanes are obtained from the addition of phenylcarbene derived from *(40)* to noncentrosymmetric olefins, the sterically more hindered, less stable *syn* isomer being formed preferentially. Similar results are obtained with phenylcarbene generated from phenyldiazomethane[32] and quantitative studies of epimer ratios attest to the similarity of the species derived from the two independent sources[11]. It should be noted that phenylcarbene generated from *(40)* adds in a highly stereoselective manner to *cis*-2-butene. Insertion selectivity ratio obtained for phenylcarbene generated from *trans*-stilbene oxide *(40)* with respect to aliphatic primary and aliphatic secondary C—H bonds also compares favorably with the results obtained using phenyldiazomethane[11, 29]. Although no ESR signal corresponding to phenylcarbene could be detected[30], the typical luminescence at 389 and 414 nm due to this species is observed at 77 °K upon irradiation of *(40)* and *(41)* in 3-methylpentane glasses[31].

The fragmentation of the unsymmetrical oxirane *(42)* may occur by two routes. Comparison of the respective phosphorescences of the carbonyl fragments resulting from irradiation of triphenyloxirane *(42)* in 3-methylpentane glass at 77 °K with those of a standard containing equimolar amounts of benzophenone and benzaldehyde indicates that the latter represents the preferred mode of fragmentation (≈70%)[31b]. The relative amounts of benzhydryl and benzyl methyl ether formed from *(42)* (85 and 15%, respectively) when methanol is employed as a trapping agent supports the conclusion that cycloelimination occurs preferentially to give diphenylcarbene *(18)* and benzaldehyde[34]. The emission characteristic of diphenylcarbene at 485 nm is observed upon irradiation of *(42)* in 3-methylpentane glass. The ESR signal of triplet diphenylcarbene *(18)* also is observable upon photolysis of *(42)* at 77 °K[30].

Table 3. Examples of photocycloeliminations from oxiranes.

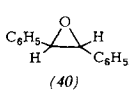
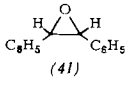
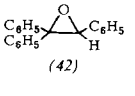
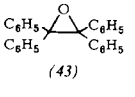
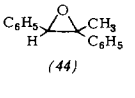
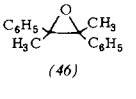
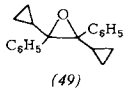
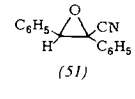
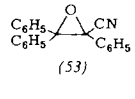
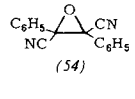
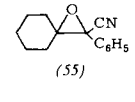
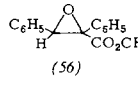
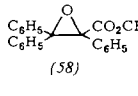
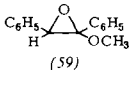
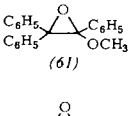
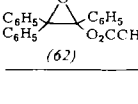
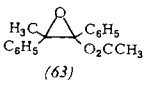
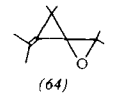
Oxirane	Carbene	Yield (%)	Ref.
 *(40)*	$C_6H_5\ddot{C}H$ *(11)*	90, 65–70 [a]	[11, 27, 28, 30, 31]
 *(41)*	$C_6H_5\ddot{C}H$ *(11)*	not reported	[31]
 *(42)*	$(C_6H_5)_2C$: *(18)* $C_6H_5\ddot{C}H$ *(11)*	85 [b] 15 [b]	[27, 30, 31]
 *(43)*	$(C_6H_5)_2C$: *(18)*	88–100 [b]	[27, 30, 31]
 *(44)*	$C_6H_5\ddot{C}CH_3$ *(45)* $C_6H_5\ddot{C}H$ *(11)*	not reported	[33a]
 *(46)*	$C_6H_5\ddot{C}CH_3$ *(45)*	40–60 [a]	[31, 34]
 *(47)*	$[C_6H_5CO(CH_2)_4\ddot{C}C_6H_5]$ *(48)*	detected spectroscopically	[31, 33b]
 *(49)*	 *(50)*	75 [b]	[33c]
 *(51)*	$C_6H_5\ddot{C}CN$ *(52)* $C_6H_5\ddot{C}H$ *(11)*	62 [b] ≈5 [b]	[35, 36, 39]
 *(53)*	$C_6H_5\ddot{C}CN$ *(52)* $(C_6H_5)_2C$: *(18)*	71 [b] ≈5 [b]	[35, 37]
 *(54)*	$C_6H_5\ddot{C}CN$ *(52)*	60–65 [a]	[37, 38, 41]
 *(55)*	$C_6H_5\ddot{C}CN$ *(52)*	15 [b], 20 [a]	[35]
 *(56)*	$C_6H_5\ddot{C}CO_2CH_3$ *(57)*	20 [a]	[37, 42]
 *(58)*	$C_6H_5\ddot{C}CO_2CH_3$ *(57)* $(C_6H_5)_2C$: *(18)*	40 [a] traces [a]	[37]
 *(59)*	$C_6H_5\ddot{C}H$ *(11)* $C_6H_5\ddot{C}OCH_3$ *(60)*	principal product ≈5	[41, 43]
 *(61)*	$(C_6H_5)_2C$: *(18)*	75 [b]	[33c, 43]
 *(62)*	$(C_6H_5)_2C$: *(18)*	principal product	[33c]

Table 3. Examples of photocycloeliminations from oxiranes.

Oxirane	Carbene	Yield (%)	Ref.
 *(63)*	$C_6H_5\ddot{C}CH_3$ *(45)*	40 [b]	[33c, 34a]
 *(64)*	 *(65)*	[c]	[44]

[a] Based on addition to alkenes to give cyclopropanes.
[b] As determined by the extent of insertion in alkanes and/or methanol.
[c] Proposed intermediate.

Upon irradiation in methanol/benzene tetraphenyloxirane *(43)* gives benzhydryl methyl ether in essentially quantitative yield[27]. Both benzophenone and diphenylcarbene are observable upon irradiation of this substrate in a rigid glass at 77 °K as described above[30,31b].

2-Methyl-2,3-diphenyloxirane *(44)* also fragments in two ways to give phenylcarbene *(11)* and phenylmethylcarbene *(45)*[33a]. *trans*-2,3-Dimethyl-2,3-diphenyloxirane *(46)* is a superior source of phenylmethylcarbene *(45)*, which is trapped as α-phenethyl methyl ether in methanol. The yields of phenylcyclopropanes which result upon irradiation of *(46)* in alkenes range from 40—60%[34].

A phosphorescence similar to that of acetophenone is apparent in the luminescence spectrum of an irradiated sample of 1,2-diphenyl-1,2-epoxycyclohexane *(47)* and upon warm-up of the matrix an emission similar to *trans*-stilbene appears[31b]. These data suggest that opening occurs to the expected ketocarbene *(48)*; however, the photostability of *(47)* and its lower homolog in solution suggests that under these conditions recyclization is efficient[33b].

Irradiation of *trans*-2,3-diphenyl-2,3-dicyclopropyloxirane *(49)* in methanol affords cyclopropylphenylcarbene *(50)*, trapped as α-cyclopropylbenzyl methyl ether[33c]. A variety of oxirane precursors for cyanophenylcarbene *(52)* have been investigated including *(51)*, *(53)*, and *(54)* which possess synthetic utility[35,37,39,41]. When methanol is employed as a trapping agent α-cyanobenzyl methyl ether is found to be produced in high yield. These oxiranes [in particular *(53)* and *(54)*] appear to be superior to diazophenylacetonitrile as a precursor for *(52)*[40] and photolyses conducted in 2,3-dimethyl-2-butene afford 1-cyano-2,2,3,3-tetramethyl-1-phenylcyclopropane in relatively high yield. In those cases such as *(51)*, *(53)*, and *(55)* where the substitution pattern is unsymmetrical a decided preference for cycloelimination of cyanophenylcarbene *(52)* is apparent as evident from the data in Table 3. In the case of *(51)* the photoelimination of phenylcarbene *(11)* was confirmed by ESR spectroscopy[33d]. The spirooxirane *(55)* represents the only photolabile substrate of this type found to date which undergoes cycloelimination in the absence of *vicinal* diaryl ring substitution.

Photolysis of the glycidic esters *(56)* and *(58)* in 2,3-dimethyl-2-butene affords 1-methoxycarbonyl-2,2,3,3-tetramethyl-1-phenylcyclopropane (20 and 40%, respectively) and the expected oxetanes of the alkene and benz-

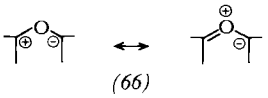
aldehyde or benzophenone[37,42]. Furthermore methoxycarbonylphenylcarbene *(57)* formed from *(56)* is trapped by methanol to give α-methoxycarbonylbenzyl methyl ether and with 2-methyl-2-butene the epimeric 1-methoxycarbonyl-1-phenyl-2,2,3-trimethylcyclopropanes. A minor product in the latter case is 1,1,2-trimethyl-3-phenylcyclopropane[37,42].

2-Methoxy-2,3-diphenyloxirane *(59)* conceivably could undergo cycloelimination to methoxyphenylcarbene and benzaldehyde and/or phenylcarbene and methyl benzoate. Irradiation of *(59)* in 2-methyl-2-butene and 2,3-dimethyl-2-butene confirms that the preferred mode of cleavage is to phenylcarbene and methyl benzoate[41,43]. Photocycloelimination also is essentially unidirectional in the case of 2-methoxy-2,3,3-triphenyloxirane *(61)*[33c]; in methanol the methyl ether of benzhydrol is the major adduct. Luminescence and ESR studies confirm the intermediacy of diphenylcarbene. No evidence was obtained for cycloelimination to give benzophenone and methoxyphenylcarbene which, by analogy with other related systems, should give the dimethylacetal of benzaldehyde upon reaction with methanol[33c]. These results are consistent with those reported independently by *Temnikova* and *Stepanov*[43].

As anticipated on the basis of the behavior of the structurally related oxiranes *(59)* and *(61)*, 2-acetoxy-2,3,3-triphenyloxirane *(62)* undergoes photocleavage to give diphenylcarbene. No products derived from phenylacetoxycarbene were detected[33c]. Similarly, *trans*-2-methyl-2,3-diphenyl-3-acetoxyoxirane *(63)* photofragments to methylphenylcarbene and the mixed anhydride of benzoic and acetic acids[33c,34a].

Irradiation of the oxaspiropentane *(64)* in benzene results in generation of several products. A cyclopropylcarbene *(65)* formed by elimination of acetone from *(64)* is invoked to rationalize the formation of tetramethylcumulene[44].

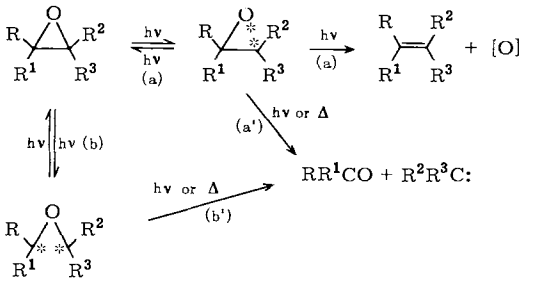
The preferred modes of fragmentation for the unsymmetrical polar substituted aryloxiranes *(51)*, *(53)*, *(56)*, *(58)*, *(59)*, *(61)*, *(62)*, and *(63)* may be predicted if a zwitterionic intermediate such as *(66)* is assumed. The overall cycloelimination is thus viewed as a photo-induced or thermal α-elimination of the carbonyl fragment from



(66)

the more stable possible zwitterion formed by initial C—C oxirane bond cleavage. Further study is required to establish whether this heuristic argument has valid theoretical implications.

The mechanistic pathways delineated in Scheme 1[31b] are consistent with the ESR and optical spectroscopic as well as chemical experimental observations made to date on oxirane substrates. While alkenes are not detected among the solution photoproducts of oxiranes at ambient temperatures they are nevertheless found to be produced at 77 °K in rigid glasses by an intramolecular oxygen extrusion process [path (a)]. It has been proposed that at ambient



Scheme 1. The asterisks are employed to avoid any specific inference with respect to the electronic nature (and/or multiplicity) of the intermediates.

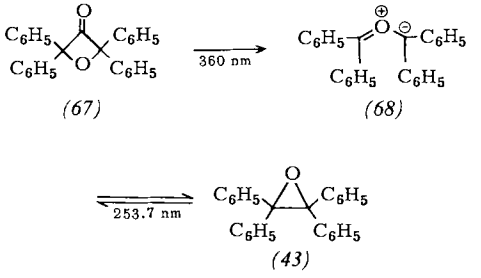
temperatures the reaction rate *via* path (a') may be so fast that it completely dominates the photochemistry of the oxirane. However, as the temperature is lowered, the rates of reaction by paths (a) and (a') become comparable and the products of both reactions are observed[31b]. Further studies in this area are in progress.

2.4. Photochromic Behavior of Vicinal Diaryloxiranes

The low temperature photochromic behavior observed for vicinally substituted diaryloxiranes appears to be related to the photocycloelimination reactions. Colors are produced upon irradiation of 2,3-diaryloxiranes in rigid glasses at 77 °K. The colors are stable at 77 °K; however, bleaching occurs upon warming above 140 °K or upon irradiation into the visible absorption bands[31b]. Arylcarbenes and carbonyl compounds are formed to some extent simultaneously and may be observed in the presence of the colored species using optical and ESR spectroscopic techniques. The extent of cycloelimination observed during photolysis warm-up cycles is estimated to be 20—25 times more than originally produced in the initial photolysis[45].

Although the thermal production of additional carbene and bleaching of the color upon warming to near 140 °K occur essentially simultaneously, it is possible that the colored intermediate is not that species from which the additional carbene is derived at least by thermal cleavage. This is clearly apparent from recent work by *Huisgen (vide infra)* and our own work.

We have been able to show that, at λ = 360 nm, 2,2,4,4-tetraphenyl-3-oxetanone *(67)* may be photodecarbonylated under conditions where the oxirane *(43)* is photostable

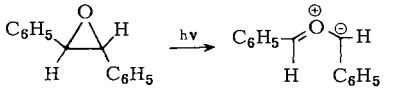


(67) *(68)* *(43)*

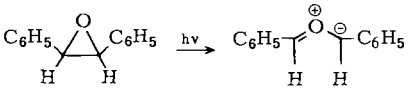
to form a colored intermediate, spectroscopically identical to that obtained from *(43)* at shorter wavelength (λ = 253.7 nm). At the longer wavelength no diphenylcarbene *(18)* is formed from *(67)* even in solution at ambient

temperatures[33e,45]. The formation of a common intermediate *(68)* from *(67)* and *(43)* implicates C—C bond scission in the oxirane photochromic process; *thermal* cleavage of *(68)* appears unfavorable since further fragmentation does not occur at 40 °C.

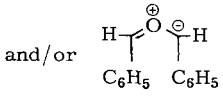
The ring opening of oxiranes to give colored ylides is subject to orbital symmetry constraints and evidence has been presented by *Do-Minh*, *Trozzolo*, and *Griffin*[45] that the process occurs photochemically in a concerted disrotatory manner. The symmetry allowed transformations are exemplified using *cis*-stilbene oxide *(41)*.



(40) *(69)*



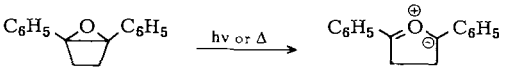
(41) *(70a)*



(70b)

Thermodynamic considerations dictate the mode of disrotation in those cases such as *(41)* where "inward" and "outward" alternatives to give *(70b)* and *(70a)*, respectively, exist. The *exo* ylide *(70a)* is more stable than the other possible structural isomer having *endo* stereochemistry, *(70b)*, and for that matter than the ylide *(69)* obtained from the *trans* isomer *(40)*. The visible spectral absorption maximum of the colored intermediate obtained from *(41)* is red-shifted relative to that from *(40)* which presumably reflects the predominant formation of *(70a)* rather than *(70b)*. Furthermore these conclusions are supported by the work of *Huisgen* and co-workers[46] who have trapped an azomethine structurally related to *(70a)* and derived from a *cis* aziridine *via* the "outward" disrotatory mode.

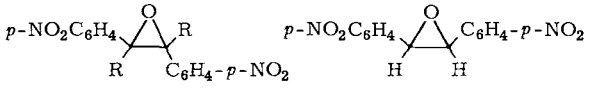
Direct evidence for the formation of a carbonyl ylide from an oxirane was obtained by *Arnold* and *Karnischky*[47]. Photolysis or pyrolysis (100 °C) of 5-oxabicyclo[2.1.0]-pentane *(71)* gave purple species whose visible absorption spectra were essentially identical. It is proposed that the carbonyl ylide *(72)* is responsible for the purple color.



(71) *(72)*

The oxiranyl ring of *(71)* is incorporated in a fused system which is geometrically constrained to open in a disrotatory manner. Strain is relieved upon bond cleavage which must account for the facile thermal conversion of *(71)* into *(72)* (in violation of orbital symmetry predictions) and the stability of the latter. The colored intermediate may be trapped using conventional dipolarophiles. Previous work in our laboratory had shown that no such behavior is exhibited by the higher homolog *(47)* and the analogous 6-oxabicyclo[3.1.0]hexane[31,33f].

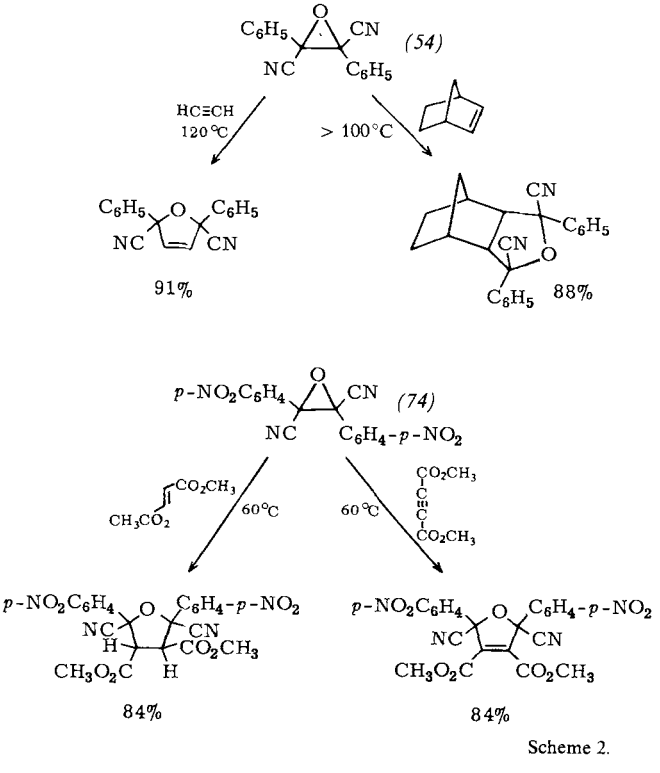
Recently *Huisgen* and co-workers[48] have trapped the carbonyl ylides that are present in thermal equilibrium with several aryloxiranes, including the *cis* and *trans* forms of *(51)* and *(53)*, as well as *(73)*—*(75)*, with a variety of dipolarophiles. The stereochemistry of addition in each case is explicable within the framework of orbital symmetry theory.



(73), R = H
(74), R = CN

(75)

Selected examples of the adducts, isolated in high yield, are shown in Scheme 2; the temperature at which oxirane ring cleavage occurs is remarkably low.



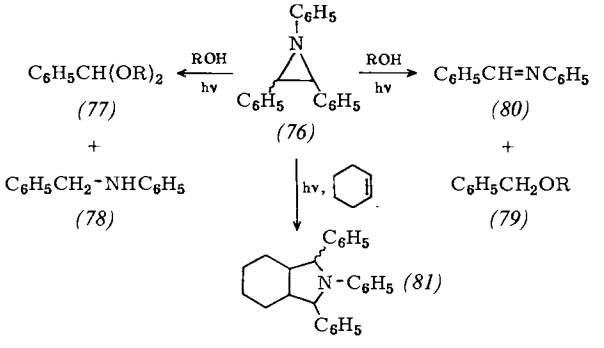
Scheme 2.

Huisgen and co-workers failed to detect phenylcyanocarbene or its reaction products upon heating of oxiranes such as *(51)* or *(53)* to 160 °C, despite equilibration with carbonyl ylides. Thus the latter do not fragment; this is in accord with our observation that tetraphenyloxetanone *(67)* is converted photochemically into the oxirane without formation of diphenylcarbene. Our inability to detect substantial *cis-trans* photointerconversion of oxiranes and photoracemization of active *trans*-stilbene oxide at ambient temperatures in solution may therefore be due to intervention of an efficient cheletropic mechanism (concerted extrusion) under these conditions and/or the

fact that the extinction coefficient of the ylide may be sufficiently greater than that of the residual oxirane to render subsequent photocleavage of the ylide by a second photon to carbene photochemically highly probable. Another alternative is that the intermediate formed by C—O bond cleavage (Scheme 1) may be the carbene precursor. Clearly further work is required to completely define the overall mechanistic path of oxirane photocycloelimination and such is in progress[33c].

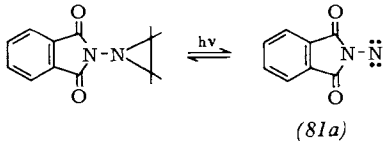
2.5. Carbenes from Aziridines

The formation of phenylcarbene upon photolysis of 1,2,3-triphenylaziridine *(76)* has been reported by *Nozaki* and co-workers[49]. Irradiation of *(76)* in alcohols results in cleavage of the aziridine ring to give benzaldehyde acetals *(77)* and *N*-benzylaniline *(78)*. Competitive cycloelimination of phenylcarbene, trapped as the alkyl benzyl ether *(79)*, appears to occur and the residual fragment *(80)* was also detected. This mode of cleavage is formally analogous to the photofragmentation of aryloxiranes.



R = CH_3, C_2H_5, 2-C_3H_7, $C(CH_3)_3$

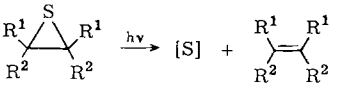
An azomethine ylide intermediate assumed to be implicated in these reactions may be intercepted with cyclohexene. A pair of stereoisomeric 1,3-cycloaddition products having the 1,2,3-triphenyloctahydroisoindole structure *(81)* are formed. No evidence was found to indicate that phenylnitrene is generated from *(76)*. Similarly attempts to generate phenylnitrene from 1,2,2,3-tetraphenylaziridine proved unsuccessful[33g]. In contrast, the amino nitrene *(81a)* was readily liberated upon irradiation of the corresponding aziridine and undergoes transfer to other olefins[49a]



(81a)

2.6. Cycloeliminations of Thiiranes

Despite their superficial resemblance to aryloxiranes, the photolytic cycloelimination reactions of arylthiiranes *(82)* do not parallel the behavior of the former. A [3→2+1] photocycloelimination to sulfur and alkenes *(83)* appears to be the preferred mode of cleavage; no carbene was detected (Table 4).



(82) *(83)*

Table 4. Examples of photocycloeliminations from thiiranes *(82)*.

Thiirane	R^1	R^2	Ref.
a	H	C_6H_5	[50]
b	C_6H_5	C_6H_5	[31b, 33b]
c	C_6H_5	C_6H_5CO	[51, 52]
d	2,2'-biphenylylene		[33b]
e	2,2'-oxydiphenyl		[33b]

2.7. Cycloeliminations of Oxaziridines

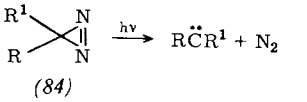
A priori two [3→2+1] cycloelimination reactions might be anticipated for oxaziridines; path (a) to give carbenes and nitroso compounds and/or path (b) to give nitrenes and carbonyl compounds.



In those cycloeliminations reported by *Meyer* and *Griffin*[53] and *Splitter* and *Calvin*[54] the reaction invariably proceeds by the latter mode. The arylnitrenes formed from the oxaziridines (or nitrones *via* prior cyclization) have been trapped chemically using substituted amines[53] and detected spectroscopically independently by *Calvin* and co-workers[54] and *Griffin* and *Trozzolo*[33h] using ESR techniques.

2.8. Carbenes from Diazirines

The photochemistry of diazirines *(84)*, established carbene precursors, has been reviewed extensively elsewhere[55,56].



(84)

Irradiation of these cyclic isomers of diazo compounds results in loss of nitrogen and generation of the corresponding carbene. The diazirines whose photodecompositions have been described to date together with the carbene generated in the primary process are summarized in Table 5. The majority of these investigations were conducted in the gas phase and numerous secondary reactions occur.

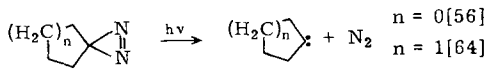
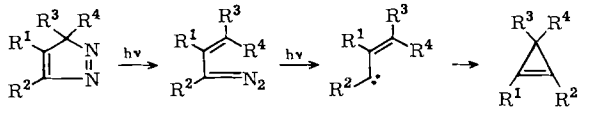


Table 5. Carbenes $R\ddot{C}R^1$ as primary products of photocycloelimination from diazirines *(84)*.

R	R^1	Ref.
H	H	[57, 58]
F	F	[56]
CH_3	CH_3	[60]
C_2H_5	C_2H_5	[62]
CH_3	H	[59]
CH_3	C_2H_5	[61, 62]
2-C_3H_7	H	[62]
2-C_3H_7	CH_3	[62]
$C(CH_3)_3$	H	[62]
$C(CH_3)_3$	CH_3	[62, 63]
n-C_5H_{11}	H	[62]
C_6H_5	Br	[65]

3. [5→3+2] Cycloeliminations

The photochemical conversion of substituted 3*H*-pyrazoles *(85)* to cyclopropenes *(88)*, which formally may be viewed as a [5→3+2] cycloelimination, is believed to occur by a two photon process. The first step involves formation of the diazoalkane *(86)*, which subsequently loses nitrogen to give a vinyl carbene *(87)*, the immediate precursor of the cyclopropene *(88)*[66,67].



(85) *(86)* *(87)* *(88)*

Those 3*H*-pyrazoles whose conversion to cyclopropenes has been investigated are listed in Table 6. That the penultimate intermediate is the diazoalkane *(86)* is suggested by a transient red coloration during the photolyses[66,68,72]. Direct evidence for the diazo intermediate was obtained by irradiation of the trimethyl-3*H*-pyrazole *(85a)* using a filter which eliminates both visible light and ultraviolet light below 320 nm[68]. Under these conditions the expected diazoalkane is formed in 50% yield.

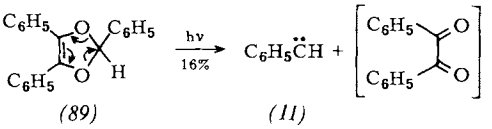
Table 6. Carbenes *(87)* and cyclopropenes *(88)* by photocycloelimination from 3*H*-pyrazoles *(85)*.

	R^1	R^2	R^3	R^4	Ref.
a	H	CH_3	CH_3	CH_3	[68, 69]
b	CH_3	CH_3	CH_3	CH_3	[68]
c	H	C_2H_5	CH_3	CH_3	[68]
d	H	$C(OH)(CH_3)_2$	CH_3	CH_3	[67]
e	—$(CH_2)_4$—		CH_3	CH_3	[66, 68]
f	—$(CH_2)_5$—		CH_3	CH_3	[66, 68, 69]
g	3-CH_3O_2C-benzo[*c*]		CH_3	CH_3	[70]
h	CH_3	CH_3	CH_3	OCH_3	[68]
i	CH_3O_2C	CH_3O_2C	2,2'-biphenylylene		[71]

Bentrude[72] has reported that 1,3,2-dioxa-P^v-phospholes undergo photocycloelimination of the [5→3+2] and [5→4+1] types. The former reaction is assumed to give ketocarbenes; however, these intermediates were not trapped.

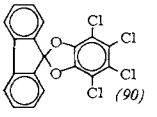
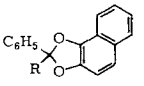
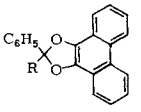
4. [5→4+1] Cycloeliminations

Generation of arylcarbenes from substituted 1,3-dioxolanes by [5→4+1] cycloelimination reactions of the type depicted for *(89)* have been reported by *Griffin* and coworkers[73]. Additional examples are summarized in Table 7.



(89) *(11)*

Table 7. Examples of photocycloeliminations from dioxolanes. The yields were determined from the extent of ether formation in alcohols.

Dioxolane	Arylcarbene	Yield (%)
 *(90)*	9-fluorenylidene *(91)*	30
 *(92a)*, R = H *(92b)*, R = C_6H_5	$C_6H_5\ddot{C}H$ *(11)*	17
	$(C_6H_5)_2C$: *(18)*	11
 *(93a)*, R = H *(93b)*, R = C_6H_5	$C_6H_5\ddot{C}H$ *(11)*	15
	$(C_6H_5)C$: *(18)*	5

5. [5→2+2+1] Cycloeliminations

A variety of 1,3-dioxolanes such as *(94)* undergo cycloelimination of the [5→2+2+1], rather than [5→4+1] type; *i.e.*, it is not invariably the ring carbon atom flanked by the oxygen atoms which is extruded in the divalent form. The course of the reaction may be altered by incorporating a trigonal center or heteroatom in position 2. This mode of cycloelimination is observed in the case of several 1,3-dioxolanes[29,74,75] (Table 8).

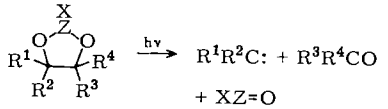
Irradiation of the cyclic arylcarbonates *(94a)*—*(94e)* results in photofragmentation to arylcarbenes, carbonyl compounds, and carbon dioxide[29,74]. Diphenylcarbene *(18)*, trapped as benzhydryl methyl ether, is formed in 60% yield upon photolysis of *(94a)* in methanol. The sulfite *(94a)* also affords *(18)* in high yield (≈40%) upon irradiation in methanol[74]. The other fragments in this case are benzophenone and sulfur dioxide. Tetraphenyloxirane *(43)* could not be detected among the photolysis products of either *(94a)* or *(94b)*.

A [5→2+2+1] cycloelimination reaction yielding carbene and carbonyl compound has been reported by *Bischoff* and *Brandstaedter*[76]. Photolysis of 3,5-dimethyl-3,5-dihydroxy-1,2-dioxolane *(95a)* gives formic acid which is formulated as arising from methylene. Irradiation of the related 4,4-dichloro compound *(95b)* in cyclohexene

Table 8. Examples of photocycloelimination from dioxolanes *(94)*.

	Z	X	R^1	R^2	R^3	R^4	Carbene		Yield (%)	Ref.
a	C	O	C_6H_5	C_6H_5	C_6H_5	C_6H_5	$(C_6H_5)_2C$:	*(18)*	60 [a]	[74]
b	C	O	H	C_6H_5	C_6H_5	H	$C_6H_5\ddot{C}H$	*(11)*	3.8 [b]	[29]
c	C	O	H	C_6H_5	H	C_6H_5	$C_6H_5\ddot{C}H$	*(11)*	5.2 [b]	[29]
d	C	O	CH_3	C_6H_5	CH_3	C_6H_5	$C_6H_5\ddot{C}CH_3$	*(45)*	not determined	[34a]
e	C	O	CH_3	C_6H_5	C_6H_5	CH_3	$C_6H_5\ddot{C}CH_3$	*(45)*	not determined	[34a]
f	S	O	C_6H_5	C_6H_5	C_6H_5	C_6H_5	$(C_6H_5)_2C$:	*(18)*	40 [a]	[74]
g	S	O	H	C_6H_5	C_6H_5	H	$C_6H_5\ddot{C}H$	*(11)*	5.5 [b]	[29]
h	S	O	H	C_6H_5	H	C_6H_5	$C_6H_5\ddot{C}H$	*(11)*	6.6 [b]	[29]
i	S	O	CH_3	C_6H_5	CH_3	C_6H_5	$C_6H_5\ddot{C}CH_3$	*(45)*	not determined	[34a]
j	S	O	CH_3	C_6H_5	C_6H_5	CH_3	$C_6H_5\ddot{C}CH_3$	*(45)*	not determined	[34a]
k	P	$3\ OC_2H_5$	C_6H_5	CN	CN	C_6H_5	$C_6H_5\ddot{C}CN$	*(52)*	60–70 [c]	[75]
l	P	$3\ OC_2H_5$	2,2'-biphenylylene		2,2'-biphenylylene		9-fluorenylidene	*(91)*	not reported	[75]

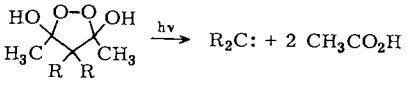
[a] From extent of ether formation in alcohols.
[b] By extent of C—H insertion.
[c] Based on addition to alkenes to give cyclopropanes.



$$\xrightarrow{h\nu} R^1R^2C: + R^3R^4CO + XZ{=}O$$

(94)

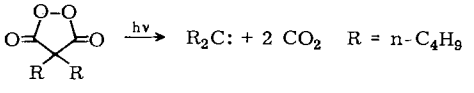
gives 7,7-dichloronorcarane in 0.4% yield which supports the contention regarding *(95a)*.



$$\xrightarrow{h\nu} R_2C: + 2\ CH_3CO_2H$$

(95a), R = H
(95b), R = Cl

Slightly better yields of carbene (5—8%) were obtained upon irradiation of *(96)*; nevertheless, other photochemical processes dominate in this case too[77].



$$\xrightarrow{h\nu} R_2C: + 2\ CO_2 \quad R = n\text{-}C_4H_9$$

(96)

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The Anomalous Temperature Dependence of Enzyme-Catalyzed Reactions[**]

By Gerhard Talsky[*]

Breaks or curvatures in the plot of log v_{br} vs. $1/T$ have been described in the literature for a number of reactions. If sufficiently small temperature intervals are used in the investigation of the temperature dependence (STI method) a trend line is obtained instead. It is then possible to distinguish regions of linear behavior and regions of anomalous behavior. The effects of e.g. the pH, the ionic strength, and added salts as well as of the size of the enzyme and substrate molecules on the anomalies were examined. The anomalous temperature dependence of the reaction rate was found to be a particularly sensitive indicator of the reaction event on the enzyme. The course of the reaction is evidently affected even by relatively small changes in conformation, particularly in the region of the active center.

1. Introduction

The temperature dependence of the rate constant k of chemical reactions is generally described by the Arrhenius equation [eq. (1) and (2)]:

$$k = A\,e^{-E_{exp}/RT} \tag{1}$$

$$\ln k = \ln A - E_{exp}/RT \tag{2}$$

If a plot of $\ln k$ against $1/T$ in accordance with equation (2) gives a straight line, the experimental activation energy E_{exp} can be calculated from the slope of that line. In simple reactions, E_{exp} contains the true activation energy as well as the temperature dependence of all the reaction parameters.

However, enzyme reactions are not simple reactions, but consist of a series of partial steps. For example, the enzymatic hydrolysis of an ester can be represented schematically as indicated by equation (3):

$$\mathrm{EH + AcOR} \rightleftharpoons \mathrm{(EHAcOR)} \rightleftharpoons \mathrm{(EHAcOR)_1^* \cdots (EHAcOR)_i^*} \rightleftharpoons \mathrm{(EAcHOR)^*} \rightleftharpoons \mathrm{(EAcHOR)} \rightleftharpoons \mathrm{EAc + HOR} \tag{3a}$$

$$\mathrm{EAc + H_2O} \rightleftharpoons \mathrm{(EAcH_2O)} \rightleftharpoons \mathrm{(EAcH_2O)_1^* \cdots (EAcH_2O)_i^*} \rightleftharpoons \mathrm{(EHAcOH)^*} \rightleftharpoons \mathrm{(EHAcOH)} \rightleftharpoons \mathrm{EH + AcOH} \tag{3b}$$

The enzyme (EH) and the acyl ester (AcOR) initially form an adsorption complex, the Michaelis complex, which is activated by a change in conformation. The acylenzyme (EAc), which can actually be isolated under favorable circumstances, is then formed *via* at least two steps[1]. EAc is then converted in the presence of water into the enzyme-product complex (EHAcOH), again by a number of reaction steps, and the complex, after deactivation and restoration of the original conformation of the enzyme, decomposes into the product (AcOH) and the enzyme, which can then enter into a new cycle.

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The rate constant k assumes a complex value in composite reactions of this type, and it is then composed of the rate constants of the individual steps. Even in this case, however, the temperature dependence of the rate constant of the overall reaction k_{br} as well as the overall reaction rate v_{br} which is proportional to it should obey the Arrhenius equation.

However, enzyme-substrate systems for which this is not true have been described; the most important enzymes are listed in Table 1.

Table 1. Examples of enzymes from enzyme-substrate systems whose reaction rates exhibit anomalous temperature dependence.

Oxidoreductases	*Hydrolases*
Alcohol dehydrogenase [2]	Acetylcholinesterase [9]
Bacteria dehydrogenase [3]	Lipase [10, 11]
L-Amino oxidase [4]	Trypsin [11]
Xanthine oxidase [5, 6]	Chymotrypsin [10]
Transferases	Cathepsin [10]
Phosphorylase [7]	Papain [12]
Levan saccharase [8]	Myosin ATPase [13, 14]
	Urease [15—17]
	Invertase [11]
	Lyases
	Fumarase [18, 19]

There are two basic types of anomalies, *i.e.* convex curves (continuous transition from one activation energy to another), as in the case of acetylcholinesterase[9], and two intersecting straight lines (sudden change from one activation energy to another), as in the cases of pancreas lipase[10, 11], trypsin[11], and invertase[11].

The convex course of the curve obtained when log v_{br} is plotted against $1/T$ in the case of acetylcholinesterase was attributed by *Wilson* and *Cabib*[9] to a change in rate-determining step from acetylation at low temperatures to deacetylation at higher temperatures. *Stern*[20] has discussed two successive reactions with different temperature coefficients for a curve of this type.

Sharp breaks in the Arrhenius diagram, on the other hand, cannot be explained by means of the usual kinetic concepts. According to *Kistiakowsky*[34], who carried out a critical study of the anomalous temperature dependence of reactions of urease, the activation energies of the two reactions

would have to differ by about 200 kcal/mole if the break is limited to a range of 2 °C. He therefore considers only the curved plot, and not the sharp break, to be real. *Kistiakowsky* explains the anomalies by an equilibrium between active and inactive forms of the enzyme.

2. Temperature Dependence of the Reaction Rate at Small Temperature Intervals

From the examples of anomalous temperature dependence of the reaction rate quoted in the literature we first selected the system pancreas lipase—tributyrin[*]. When the rate of the hydrolysis of glycerol esters by lipase is determined in the usual manner at intervals of 5 to 10 °C, the test points obtained in the plot of log v_{br} *vs.* $1/T$ are equally compatible with two intersecting straight lines or with a curved plot, depending on the interpretation[21] (Fig. 1a). To obtain more accurate information about the course of the curves,

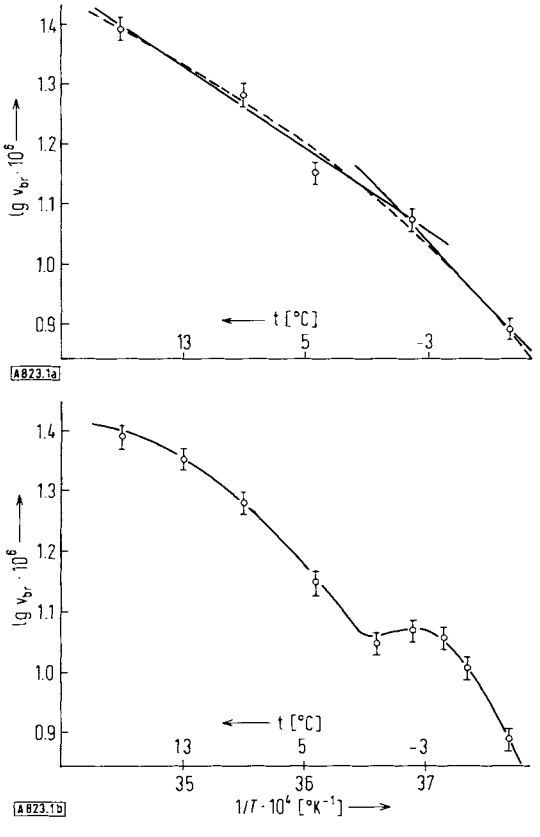


Fig. 1a. Temperature dependence of the hydrolysis of tributyrin by lipase from pig pancreas. Conditions: [substrate] = 27.3×10^{-2} mole. l^{-1}; [sodium taurocholate] = 5.95×10^{-3} mole. l^{-1}, [$CaCl_2$] = 2.4×10^{-2} mole. l^{-1}, [NH_4Cl] = 1.2×10^{-2} mole. l^{-1}, [glycol] = 4.7 mole. l^{-1}; 1 mg of lipase protein. l^{-1}, pH = 8.12, temperature intervals 4—7 °C.

Fig. 1b. Conditions as for Fig. 1a, but temperature intervals 1—2 °C.

particularly in the region of the transition between the two linear portions, we determined the reaction rate at smaller intervals (about 1 to 2 °C) and also recorded it continuously while the temperature was steadily raised or lowered.

[*] Tributyrin is glycerol tributyrate.

Careful evaluation of the results led to a conclusion that was surprising at first. A wavelike course was found in the critical temperature ranges of the curve[21–23] (Fig. 1b). If measurements are carried out in a similar manner over a wider temperature range, the result is a trend line whose very reproducible deviations from the fitted straight lines lie well outside the maximum error range of ±4% (Fig. 2)[22, 23].

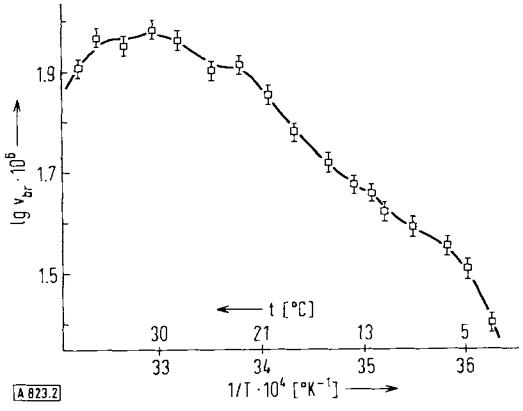


Fig. 2. Temperature dependence of the hydrolysis of tributyrin by lipase from pig pancreas. Conditions: [substrate] = 20.5×10^{-2} mole. l^{-1}, [glycol] = 3.59 mole. l^{-1}, pH = 8.10, 1 mg of lipase protein. l^{-1}.

To record the time-concentration curves automatically, we used an Autotitrator (Radiometer, Copenhagen) with glass-calomel electrodes[22]. The pH was kept constant (pH-stat) and the acid liberated was titrated automatically with 0.02 N NaOH under nitrogen. The initial rates v_0 were found in this way.

The reality of the anomalies found by us was established in various ways:

(a) The deviations of some experimental points from a fitted straight line were much greater than the experimental error determined[23];

(b) the reproducibility of the deviations was good when the same enzyme preparations were used[24, 27];

(c) even when the temperature was raised continuously, the reaction rate did not increase steadily in accordance with an exponential function, but exhibited discontinuities[21]; and finally

(d) the hydrolysis of the substrate *without* enzyme proceeded normally in accordance with the Arrhenius equation.

The question why such effects were not observed earlier can be answered as follows. In normal kinetic measurements, one usually determines only a few experimental points at fairly large intervals for use in the calculation of the activation energy; deviations were treated as errors and disregarded. Moreover, the reaction was carried out in the presence of fairly large quantities of buffers or salts, which often reduce the anomalies. It is therefore quite understandable that anomalous curves were not found *e.g.* by *Bender et al.*[35] with acetyltrypsin or by *Follman et al.*[36] with ribonuclease.

Having verified the anomalous temperature dependence of the hydrolysis of tributyrin by lipase, we then examined

the possibility of influencing the anomalous regions by varying the reaction conditions and systems in order to find out more about the reason for and basis of this phenomenon.

3. Modification of the Anomalous Regions

3.1. Sizes of the Enzyme and Substrate Molecules

On comparison of the anomalous temperature dependence of reactions of urease (MW 473000[24]) and xanthine oxidase (MW 290000[25]) with that of reactions of papain (MW 20700[26]), trypsin (MW 23800[21,27]), and chymotrypsin (MW 21000[21,27]), it is found that the course of the curve, which can almost be described as "harmonically oscillating" for enzymes with higher molecular weights, becomes more irregular at lower molecular weights. The same is true of the substrates. In the case of trypsin or chymotrypsin, for example, if N^{α}-benzoyl-L-argininamide, N^{α}-benzoyl-L-arginine ethyl ester, and tyrosine ethyl ester are used as substrates instead of the high molecular weight casein, which is itself structured, linear regions appear between the sections of anomalous behavior. This is also found for the system ribonuclease—cyclic cytidine-2',3'-monophosphate[28]. With enzymes having relatively low molecular weights and simple low molecular weight substrates, the regions of normal and anomalous temperature dependence are evidently separated. Because of their greater simplicity, systems of this type are better suited to the investigation of the anomalies. This is illustrated in Figure 3 for the case of trypsin and xanthine oxidase.

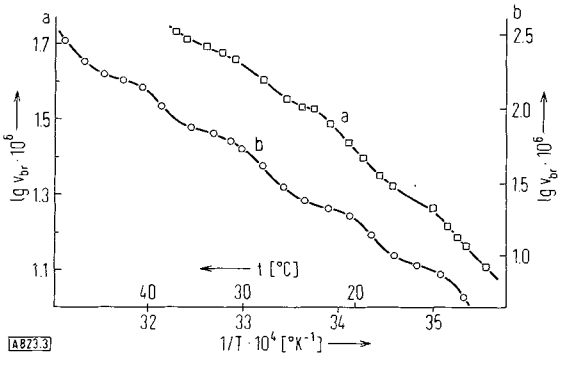


Fig. 3. Curve a: Temperature dependence of the cleavage of N^{α}-benzoyl-L-arginine ethyl ester by trypsin. Conditions: [substrate] = 3.8×10^{-3} mole. l^{-1}, [trypsin] = 1 mg. l^{-1}, pH = 9.6. Curve b: Temperature dependence of the oxidation of salicylaldehyde by xanthine oxidase. Conditions: [salicylaldehyde] = 1.5×10^{-2} mole. l^{-1}, [phosphate buffer, pH = 7.4] = 5×10^{-2} mole. l^{-1}, [methylene blue] = 6.25×10^{-5} mole. l^{-1}, [xanthine oxidase] = 18 µg. ml^{-1}.

3.2. Modified Enzymes

It is known from comparative biochemical studies that homologous proteins and enzymes usually differ slightly in their physical or immunological properties according to individual, organ, or source (animal, plant, bacterium, or fungus). Whereas the active site and certain parts of the molecule are identical for all species, changes in the amino acid sequence occur at other parts of the molecule[29]. Enzymes of this type may therefore be regarded as the simplest naturally modified enzymes.

The temperature dependence of the reaction rate of such enzymes, *e.g.* trypsin from pig pancreas and from bovine pancreas shows the same "basic curve characteristics" but though the structural differences are only small, the enzymes can be characterized relatively easily by the small temperature interval method (STI method, Fig. 4, curves a and c)[21]. Partially autolyzed trypsin (MW 17500) from which a part of the sequence (MW 6000) has been removed, (but not from the vicinity of the active site)[30] can also be clearly distinguished in this way, though the specific activity of such a modified enzyme is practically the same as that of the native enzyme (Fig. 4, curve b). Similar results are obtained on examination of α-, β-, γ-, and δ-chymotrypsin[31].

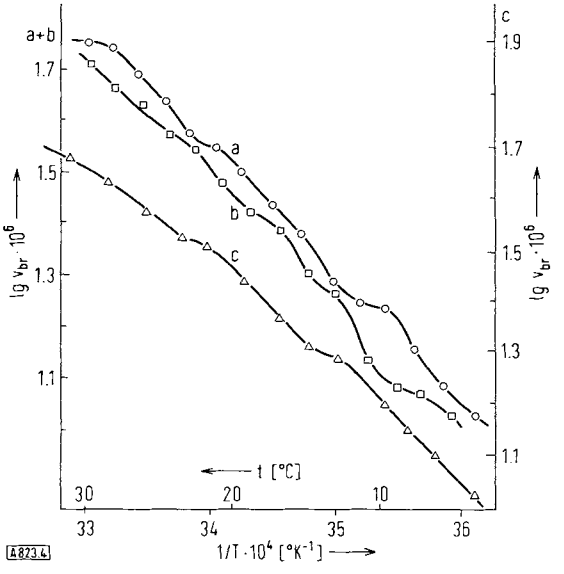


Fig. 4. Curve a: Temperature dependence of the cleavage of N^{α}-benzoyl-L-arginine ethyl ester by *pig* trypsin. Conditions: [substrate] = 3.8×10^{-3} mole. l^{-1}, [trypsin] = 1 mg. l^{-1}, pH = 9.6. Curve b: identical with a, but with partly autolyzed *bovine* trypsin having MW 17500 [30]. Curve c: identical with a, but with *native bovine* trypsin.

Chemical modification, provided that it does not affect the active site, has a similar effect on the temperature dependence of the reaction rate. Thus in the case of chymotrypsin in which two of the three terminal amino groups have been reacted with fluorescein isothiocyanate, it was possible to show that modification of the molecule even at points remote from the active site influences the anomalous ranges. The same is true if the additional terminal amino group in partially autolyzed trypsin (compared with native trypsin) is substituted or if the enzyme is acetylated[21,31].

On the other hand, if trypsin is bound either by adsorption or covalently to high molecular weight supports such as *p*-aminobenzylcellulose, the plot of log v_{br} *vs.* $1/T$ is practically linear between 10 and 50 °C[32].

3.3. Effects of the Reaction Medium

3.3.1. Homogeneous and Heterogeneous Phases

In the investigations on pancreas lipase, the reaction rate was found to be strongly dependent on the distribution of

the sparingly water-soluble glycerol ester[23]. It therefore appeared possible that the anomalies were connected with this. However, systems containing Tween 20 (a readily water-soluble lauryl sorbitan polyethylene glycol ether) as the substrate also exhibit anomalous temperature dependence, showing that the distribution of the substrate is actually of no importance to this phenomenon. This was confirmed by the later experiments with other enzyme-substrate systems, all of which proceeded in the homogeneous phase.

3.3.2. pH Value of the Reaction Medium

The rates of enzymatic reactions are usually strongly dependent on the pH value of the solution; this is attributed to the difference in the charge of the amino acids at the active site, which are important to the catalysis. We had already observed in the case of pancreas lipase[23] that an increase in the pH value, irrespective of the pH optimum of the enzyme reaction, shifts ϑ_A toward lower temperatures[*]. At the same time, the anomalous region became more significant with decreasing pH. In the trypsin-casein and trypsin-N^{α}-benzoyl-L-arginine ethyl ester systems, on the other hand, the amplitude of the curve decreased with decreasing pH. This apparently contradictory behavior becomes understandable when one considers that the isoelectric point of lipase is pH 5.2, while that of trypsin is 10.8. The anomaly is evidently intensified in the vicinity of the isoelectric point, irrespective of the pH optimum of the enzyme reaction.

3.3.3. Salt Content of the Reaction Solution

Enzymatic processes are often more or less strongly influenced by anions and cations. At low salt concentrations, specific action on the active site can lead both to acceleration and to inhibition of the reaction[21]. Larger quantities of ions, on the other hand, also lead to a nonspecific loss of activity, and ultimately to denaturing and precipitation of the protein. Whenever possible, therefore, we avoided the use of buffers and salts in our determinations. The small quantities of Na^+ and Cl^- ions introduced into the system to adjust the pH value did not interfere with the reactions under investigation, and could therefore be disregarded.

In the case of pancreas lipase, the addition of salts was found to cause a shift of ϑ_A[23]. These effects could be followed more easily in the case of the system trypsin—N^{α}-benzoyl-L-arginine ethyl ester, because of the greater simplicity and clarity of the reaction[21]. For example, 0.1 mole/l of NaCl cause an almost parallel displacement of the linear portions of the curve. This suggests that the reaction event is not affected outside the anomalous regions. On the other hand, ϑ_A does not always occur in the same position.

Trypsin behaves differently in the presence of 0.03 mole/l of $CaCl_2$, whose activity-increasing and stability-increasing action is well known. In this case, in addition to the shift of ϑ_A, the slope of the linear sections also changes, indicating that the calcium ion affects the catalytic process too.

The system ribonuclease—cyclic cytidine-2',3'-monophosphate is even more sensitive to salts. This is shown *e.g.* by the increase in the negative optical rotation of a 1.295% aqueous solution of the enzyme from $\alpha_{23}^{365} = -3.275°$ (in the absence of NaCl) to $-3.295°$ (0.033 mole/l NaCl); the optical rotation remains constant on further addition of sodium chloride (checked up to 0.1 mole/l)[21,33]. It is interesting, however, to note that as the negative optical rotation is increased by the addition of salt, the anomalies become weaker, and entirely disappear at a concentration of 0.1 mole/l; at this point, the plot of log v_{br} *vs.* $1/T$ is a straight line. In the present case at least, the changes in structure that are expressed in the change in optical rotation proceed hand in hand with the appearance of anomalies.

3.4. Partial Denaturation

We hoped to obtain further information on the anomalous temperature dependence of the reaction rate by careful denaturation of the enzymes; we expected the structure of the protein to change, but without an excessive decrease in activity.

If the activity of pancreas lipase and the temperature dependence of the hydrolysis rate are followed during incubation of the enzyme for about 38 h at 0 °C, no anomaly can be detected between 10 and 25 °C at a residual activity of 69.3%[23]. As a control, we also investigated a mixture of 70% of native and 30% of completely denatured enzyme. In this case, the anomalies were fully retained, and conversion to equal concentrations of active enzyme gave practically coincident curves.

The influence of denaturation was observed even more clearly in the hydrolysis of casein by trypsin. When the enzyme is incubated for 30 minutes at 50 °C, the amplitudes of the trend lines are higher than those obtained after incubation for 15 minutes or with free native enzyme; in contrast, after heating for 60 minutes at 50 °C, the curve obtained follows a normal course between 5 and 20 °C and exhibits a temperature optimum at 13 °C[21].

Mention should also be made of experiments carried out in the presence of 6 mole/l of urea. The added urea breaks hydrogen bonds and changes the solvation of the molecule, and this leads to unfolding and partial denaturation of the protein. Accordingly, the plot of log v_{br} *vs.* $1/T$ was only slightly curved, and showed no characteristic anomalous temperature dependence.

4. Discussion of the Anomalies

The anomalous temperature dependence of the reaction rate, which was first discovered by us for lipase[22,23], has now been observed with a total of 29 enzyme-substrate systems. In view of the deviations that occur, at least in partial regions, from the linear behavior expected from the Arrhenius equation, it must be concluded that the

[*] ϑ_A is the temperature at which the deviation from the "Arrhenius line" begins.

conditions for the Arrhenius equation, *i. e.* the independence of E_{exp} of temperature and/or the unchanged steric situation at the reaction site and in its immediate vicinity (steric factor), are not satisfied in these cases.

Let us assume, for example, that the enzyme is present simultaneously in two non-interconverting forms with different activities, possesses two active sites that catalyze the reaction with different activation energies, or could form two different activated enzyme-substrate complexes. If the two parallel reactions differ in their temperature dependence, the reaction with the greater activation energy will predominate at higher temperatures. This would give a concave plot of log v_{br} *vs.* $1/T$, but not a convex curve. However, this is exactly the opposite of the anomalies described so far, with one exception. Only *Massey*[18] gives an activation energy of 8.8 kcal/mole above 18 °C and only 5.8 kcal/mole below 18 °C for the fumarase-catalyzed hydration of fumarate at pH values above the optimum, *i.e.* pH = 7. *Patat* and *Kolb*[19], on the other hand, did not obtain an anomalous curve; they were able to explain the deviations reported by *Massey* on the basis of the temperature dependence of the extinction coefficient of fumarate (4% for every 10 °C). When this correction is applied, a uniform activation energy of 7.3 kcal/mole is obtained for pH = 7.8 (phosphate buffer).

The anomalies with continuous transition can be explained in this way, but not the sharp break (intersection of two straight lines), and much less the trend lines found by the small temperature interval technique.

For the enzymatic formation of levan, *Ebert et al.*[8] have interpreted the observed sharp break in the Arrhenius diagram of the synthesis reaction on the assumption that the overall reaction is made up of several simultaneous steps. However, this "coupled simultaneous reaction" can explain only breaks with higher values of the activation energy at lower temperatures; they cannot explain trend lines.

After the first experimental observations[22], we assumed that the anomalous behavior was due to the change in the conformation of the enzyme and hence of the enzyme-substrate complex at least in the vicinity of the active site, which proceeds in a manner comparable with a reversible phase transition. The later results supported and justified this interpretation.

If native and modified enzyme, whose active sites do not differ and which react by the same mechanism, are allowed to act on an identical substrate, the temperature dependence of the reaction rate should be the same, provided that the other part of the enzyme molecule is of no importance to the anomalies. However, since the resulting curves are different, conformational effects must be invoked as an explanation.

A relationship between the optical rotation and the anomalies in the log v_{br} *vs.* $1/T$ plot has also been detected in the hydrolysis of cyclic cytidine-2',3'-monophosphate by RNase[21, 28, 33]. Investigations on trypsin yielded similar evidence; however, the observed anomalous changes in rotation and pH were at the limit of accuracy of the measurements. No corresponding relations have so far been definitely detected with the rotatory dispersion, the fluorescence, the dielectric constant dispersion, and the behavior on differential thermal analysis.

According to these results, the conformational changes must be very small, and may even merely be changes in the positions of a few amino acids. From an estimate in which the sensitivity of the methods used was taken into account, a change of less than 5% is to be expected in the axial ratio of the globular protein.

From the observation that partially denatured enzymes exhibit normal temperature dependence of the reaction rate, as well as from the modification experiments, it is deduced that the relation between the actual catalysis and the process responsible for the anomaly is only *indirect*. Moreover, with changing pH, the maximum enzyme activity and the point at which the anomalous regions are most pronounced do not necessarily coincide. The cause of the phenomenon therefore very probably lies at the binding site of the substrate and in its vicinity.

If the initial rate v_0 at various temperatures is plotted as a function of the substrate concentration [S] for the system trypsin—N^{α}-benzoyl-L-arginine ethyl ester, one should expect the resulting "Michaelis curves" to lie synchronously one above the other. However, the v_0 values found at 15.35 °C are all lower than those found at 14.20 and 16.80 °C (Fig. 5)[21]. 15.35 °C lies precisely in the anomalous region for the overall reaction[*]. We see this as further evidence that the anomalies are due to changes in the enzyme-substrate complex.

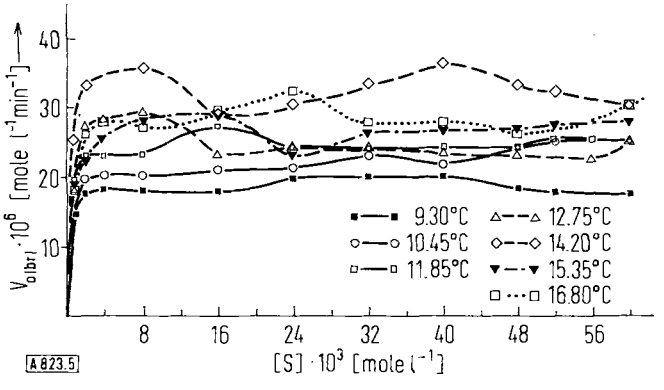


Fig. 5. Dependence of the hydrolysis of N^{α}-benzoyl-L-arginine ethyl ester (= S) by trypsin on the substrate concentration at 9.30, 10.45, 11.85, 12.75, 14.20, 15.35, and 16.80 °C. Conditions: [substrate] = 1×10^{-3} to 60×10^{-3} mole. l^{-1}, [trypsin] = 1 mg. l^{-1}, pH = 9.59.

As can be seen from Figure 5, we have here an enzyme-substrate system in which the dependence of the reaction rate on the substrate concentration does not obey the Michaelis-Menten relation. To calculate the Michaelis

[*] *B. H. Havsteen* (University of Aarhus, 1969) has detected similar anomalous regions for the temperature dependence both of the overall reaction rate and of the Michaelis constant K_m for chymotrypsin and maloamidinochymotrypsin (personal communication).

[**] K_m is a substrate constant indicating the substrate concentration at which the rate corresponds to half of the maximum value. Depending on the theory used, K_m can be expressed by rate constants of the forward and reverse reactions. According to the view of *Michaelis* and *Menten*, for example, $K_m = (k_{-1})/(k_{+1})$, while according to *Briggs* and *Haldane*, $K_m = (k_{-1} + k_{+2})/(k_{+1})$. Models in which several intermediates or covalent intermediate compounds are formulated lead to more complicated expressions (cf. *e.g.* [39, 40]).

constant K_m[**], it is necessary to use the section of the curve in the region of low substrate concentrations, since the course deviates strongly from the normal "Michaelis curve" at higher concentrations. The experimental velocity thus lies far below that calculated from the Dixon diagram. This has also been observed for other enzyme-substrate systems such as lipase—triglyceride[23], xanthine oxidase—aldehyde[25], urease—urea[24], and chymotrypsin—tyrosine ethyl ester[37,38], but will be discussed only after the investigations have been concluded.

For the hydrolysis of tyrosine ethyl ester by chymotrypsin A, on the basis of NMR measurements on the reacting substrate, *Fink* and *Patat*[38] report a sharp break in the temperature dependence of the substrate addition process at about 19 °C. However, we had found one of the anomalous regions in the log v_{br} *vs.* $1/T$ plot of the overall reaction at this temperature[21]. On the other hand, the same plot gives a straight line for the last reaction step leading to the product, *i.e.* for the postulated multicenter reaction[38].

Kinetic analysis of the hydrolysis of cyclic cytidine-2',3'-monophosphate by RNase led us to similar results (see below)[28]. Experiments are being carried out at present on the hydrolysis of esters by trypsin, in which we are investigating the formation of the enzyme-substrate complex, the acylation and deacylation, and the overall reaction independently of one another in an effort to localize the reason for the anomalies in this system more accurately[31].

Unlike in the above examples, the dependence of the reaction rate on the substrate concentration can be described by the Michaelis-Menten view for the systems lipase—Tween 20[21] and RNase—cyclic cytidine-2',3'-monophosphate[33]. A plot of K_m against $1/T$ for RNase gives two straight lines with different slopes and with a wavelike transition at the same place in the plot of log v_{br} *vs.* $1/T$[28]. The anomalies become less pronounced with increasing substrate concentration. This is as expected, since with increasing substrate saturation, the equilibrium of the formation of the activated enzyme-substrate complex has less influence on the overall reaction rate, and this becomes more distinctly a function of k_{+2}, the rate constant of the last reaction forming the product. k_{+2}, unlike K_m, is always influenced *constantly* by temperature changes, even in the anomalous region, *i.e.* a logarithmic plot of k_{+2} against $1/T$ gives a straight line[28]. The anomalous temperature dependence of the overall reaction thus depends on the contribution of the formation of the enzyme-substrate complex.

Experiments with inhibitors support the above findings. For example, anomalous regions are found as well as the normal regions in the temperature profile of the inhibition of trypsin with soybean inhibitor[31]. Moreover, a temperature anomaly is found at about 22 °C, *i.e.* in the same region as for K_m, for the constant K_p of the competitive product inhibition of RNase by the 3'-cytidylate formed[28]. This suggests that the postulated small change in conformation has a similar effect on the binding of the inhibitor and of the substrate, with the result that the course of the reaction changes.

5. Model for Description of the Temperature Anomalies

To obtain an idea of what assumptions are necessary in order to be able to describe the experimentally observed anomalous regions by means of a model, we carried out a detailed study of the course of the curve for the system trypsin—N^{α}-benzoyl-L-arginine ethyl ester between 4 and 21 °C[21,33]. This part of the curve is shown in Figure 6. If we assume that practically only $(ES)_I$ is present below T_1, only $(ES)_{II}$ above T_2, and both forms in equilibrium between T_1 and T_2, the decrease in the substrate concentration with time, *i.e.* the rate of the hydrolysis, is found to be

$$-\frac{d[S]}{dt} = A_1 e^{-(E_{exp})_I/RT}[(ES)_I] + A_2 e^{-(E_{exp})_{II}/RT}[(ES)_{II}] \quad (4)$$

S = substrate, E = enzyme, (ES) = enzyme-substrate complex, E_{exp} = experimental activation energy

where in this case $(E_{exp})_I = (E_{exp})_{II}$, but $A_1 \neq A_2$. If the anomalous region is confined to 3.28° with $T_1 = 284.9$ and $T_2 = 288.18$ °K (11.74 and 15.02 °C respectively), the enthalpy of the transition is found, after rearrangement of the van't Hoff reaction isobar, to be

$$\Delta H = \frac{2.303 R T_2 \times T_1}{T_2 - T_1} \times \log \frac{K_{T_2}}{K_{T_1}} \quad (5)$$

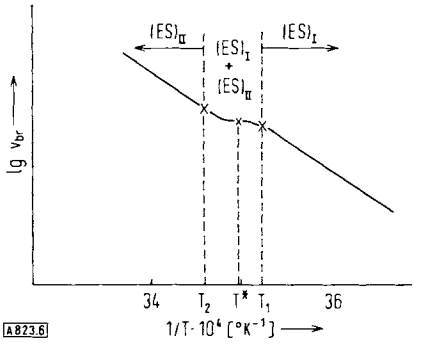


Fig. 6. Anomalous temperature dependence of the hydrolysis of N^{α}-benzoyl-L-arginine ethyl ester by trypsin. Conditions: [substrate] = 3.8×10^{-3} mole. l^{-1}, [trypsin] = 1 mg. l^{-1}, pH = 9.6. For further details see text.

If we also postulate that the concentrations of the forms I and II are 0.99 and 0.01 respectively at T_1 and 0.01 and 0.99 respectively at T_2, we find a value of 457.2 kcal/mole for ΔH; this value is too high to be understood. Similar difficulties are encountered *e.g.* in the treatment of the helix-coil transition of polypeptides or DNA. It is therefore necessary to resort to the additional assumption of cooperative processes. In this case the apparent rate constant is

$$K_{app} = K^n \quad (6)$$

where K is the equilibrium constant of the elementary process and n is the "cooperative length". The rate is then given by:

$$-\frac{d[S]}{dt} = v_{br} = e^{-E_{exp}/RT}\left[A_1 \frac{1}{1+K_{T_2(app)}} + A_2 \frac{K_{T_2(app)}}{1+K_{T_2(app)}}\right] \quad (7)$$

where

$$K_{T_2(app)} = e^{n\Delta H/R} \quad \frac{T_2 - T^*}{T_2 \times T^*} \qquad (8)$$

n = cooperative length, ΔH = bond enthalpy of *one* cooperative bond or interaction, T^* = temperature at which the concentrations of $(ES)_I$ and $(ES)_{II}$ are equal ($K_T = 1$).

Insertion of $n = 80$ and $\Delta H = 5$ kcal/mole in the above equation gives points that satisfactorily reproduce the course found experimentally for the curve (Fig. 7); it is therefore possible to give at least a formal description of the temperature dependence. However, one would then expect, contrary to observations so far with physical methods (Section 4), that a more distinct change in structure might be detected in view of the chosen "cooperative length", provided that this change was not largely confined to the interior of the folded molecule.

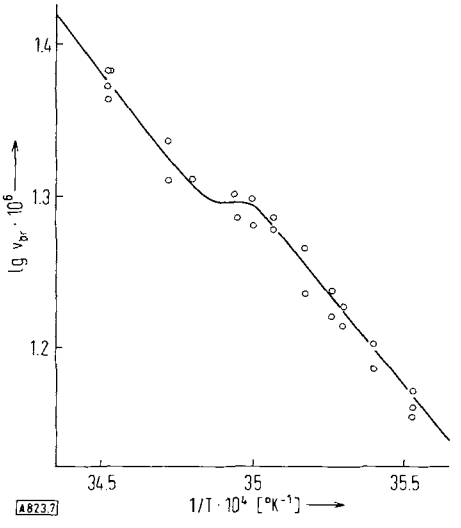


Fig. 7. Temperature dependence of the hydrolysis of N^{α}-benzoyl-L-arginine ethyl ester by trypsin. Conditions: [substrate] = 3.8×10^{-3} mole. l^{-1}, [trypsin] = 1 mg. l^{-1}, pH = 9.6.

6. Outlook

The temperature dependence of the rates of many enzyme reactions does not follow the Arrhenius equation, but follows a trend line on careful measurement at small temperature intervals. Indications of changes in the elementary processes have also been obtained from the kinetic analysis of the overall reaction. Thus by following the temperature dependence accurately, it is possible to detect small structural changes in the enzyme or in the enzyme-substrate complex with greater sensitivity than *e.g.* by measurement of the optical rotation.

It should also be possible to obtain additional information for the biotechnics of enzymatic processes. Examples are the change in the enzymes on conservation, particularly on freeze-drying, and the development of very stable enzymes for the industrial synthesis of specific chemical products.

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Tetrakis(methylmercurio)phosphonium Salts[**]

By *Dietrich Breitinger, Klaus Geske,* and *Walter Beitelschmidt*[*]

We have extended our studies of (methylmercurio)ammonium complexes[1,2] to compounds of elements of Group VB. We have prepared tetrakis(methylmercurio)-phosphonium salts $[P(HgCH_3)_4]X$, where $X = BF_4$, PF_6, or SbF_6, by the action of phosphane on methylmercury compounds CH_3HgX[3].

The IR and Raman spectra indicate point group T_d for the cation $[P(HgCH_3)_4]^+$. Assignment of the vibrations of the central PHg_4 tetrahedron (corresponding values for $[N(HgCH_3)_4]^+$ are given in parentheses) follows from the selection rules, band intensities and band form, polarization state in the Raman effect (RE) and splitting in the solid-state spectrum (site symmetry effects): ν_1 (a_1) 119 cm^{-1} (RE, polarized: $\rho \approx 0$) (141 cm^{-1}), ν_3 (t_2) 354 cm^{-1} (IR; RE, depolarized) (584 cm^{-1}), ν_4 (t_2) 54 cm^{-1} (–; RE) (66 cm^{-1}). The force constants for the P—Hg—(N—Hg) bond are estimated from the ν_1 (a_1) vibrations as $f + 3f' = 1.7_7$ mdyn·Å^{-1} (2.5_2 mdyn·Å^{-1}). The P—Hg bond is obviously weaker than the N—Hg bond.

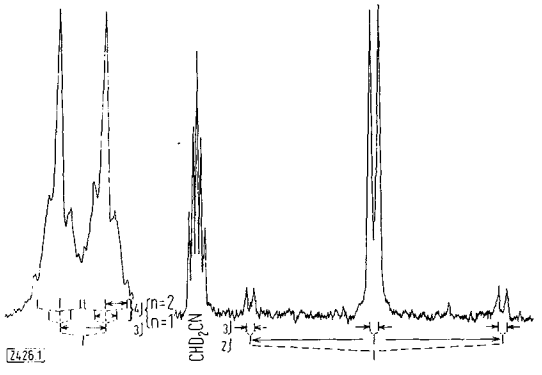


Fig. 1. ^{1}H-NMR spectrum of $[P(HgCH_3)_4]PF_6$ (saturated CD_3CN solution; 90 MHz; CHD_2CN at $\tau = 8.09$ ppm); left, main signal resolved.

In the ^{1}H-NMR spectrum[4] of $[P(HgCH_3)_4]PF_6$ (Fig. 1) the main signal is at $\tau = 9.28$ ppm (9.27 ppm). This indicates similar distribution of the cationic charge over the peripheral H atoms in the phosphonium and the ammonium complex (Pauling electroneutrality principle). The constants for the short-range coupling between ^{1}H and ^{199}Hg are found to be $^2J = J_{HgCH} = 155$ Hz (173 Hz), corresponding to the differing electronegativities of the central atoms. Coupling between the peripheral protons and the central P atom leads to a doublet splitting of main signal and satellites with $^3J = J_{PHgCH} = 4.8$ Hz. Finally, long-range coupling effects appear, due to the various nuclide compositions of the cations $[Y(^{199}HgCH_3)_n(^{200}HgCH_3)_{4-n}]^+$ (Y = N, P; $0 \leqslant n \leqslant 4$; ^{200}Hg represents all the non-coupling Hg nuclides); the coupling constants $^4J = J_{HgYHgCH} = 2.3$ Hz (3.5 Hz) are found.

X-ray analysis of single crystals of $[P(HgCH_3)_4]PF_6$ showed space group C_{2h}^5—P $2_1/c$ and the lattice parameters $a = 8.28$ Å, $b = 16.59$ Å, $c = 12.15$ Å, and $\beta = 92.3°$; with $Z = 4$, $d_{calc} = 4.17$ g·cm^{-3} to be compared with $d_{obs} = 4.12$ g·cm^{-3}. The compound was thus shown to be isotypic with the analogous ammonium salt[5]. From the number of formula units in the unit cell, from group-theoretical considerations, and from the IR spectrum of the anion the cations and anions could be assigned to general positions.

Experimental:

CH_3HgX was prepared by metathesis of AgX with methylmercury bromide in diethyl ether or 2-propanol. Phosphane was led into the solution at room temperature with exclusion of air, until the crystalline precipitate that was rapidly formed no longer increased in amount. Recrystallization from 2-propanol gave, for example, analytically pure $[P(HgCH_3)_4]PF_6$ in 10% yield (based on CH_3HgBr).

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[3] Professor *G. Schwarzenbach*, Zürich, has informed us that $[P(HgCH_3)_4]ClO_4$ (explosive) was prepared in his School some time ago but was not studied further.

[4] We thank Dr. *K. Geibel*, Institut für Organische Chemie der Universität Erlangen-Nürnberg, and Dr. *D. Scheutzow*, Institut für Organische Chemie der Universität Würzburg, for measurement of the NMR spectra.

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$H[PO_2ClF]$ and $H[PO_2BrF]$, Two New Dihalooxophosphorus Acids[**]

By *Hans Falius* and *Klaus-Peter Giesen*[*]

Of the free dihalooxomonophosphorus(v) acids, only the compounds $H[PO_2F_2]$ and $H[PO_2Cl_2]$ are as yet known, while a dibromo acid could be obtained only in the form of its salts[1]. Of the mixed dihalooxo acids only a few esters, alkylamides, and arylamides have been described[2], and the free mixed acids are all previously unknown; they cannot be prepared from organic derivatives as the phosphorus-halogen bond is cleaved by hydrolysis.

The fluorophosphorus(III) acid, $H[PHO_2F]$, obtained recently[3], appeared to be suitable as starting material for preparation of mixed halofluorophosphorus acids. Its reaction with chlorine or bromine in fact rapidly gave the two mixed dihalo acids $H[PO_2ClF]$ *(1)* and $H[PO_2BrF]$ *(2)*, respectively.

$$H[PHO_2F] + X_2 \rightarrow H[PO_2XF] + HX$$
(1); X = Cl
(2); X = Br

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Highly viscous liquids were obtained as by-products, which were not examined but presumably are polyphosphorus acids formed by condensation. Reaction with iodine is very slow; in ether it leads to red precipitates consisting, according to the reaction conditions, of red phosphorus or P_2I_4.

The acid *(1)* can also be obtained by mild partial hydrolysis of $POCl_2F$.

$$POCl_2F + H_2O \rightarrow \underset{(1)}{H[PO_2ClF]} + HCl$$

The acids *(1)* and *(2)* are liquid at room temperature and insoluble in apolar solvents. *(1)*: $d_4^{20} = 1.522\ g\,cm^{-3}$, $n_D^{20} = 1.3674$. *(2)*: $d_4^{20} = 2.140\ g\,cm^{-3}$. B. p. 215 °C was extrapolated from a few vapor pressure values for *(1)* below 40 °C; the evaporation enthalpy amounts to $\Delta H_{298} = 10900\ cal\,mol^{-1}$, and the evaporation entropy to $\Delta S_{298} = 25.1\ cal\,mol^{-1}\,°K^{-1}$. Although *(1)* is stable when moisture is excluded, *(2)* slowly becomes yellow (Br_2), especially in light. Both compounds are hydrolyzed in aqueous solution, and then consume 3 equivalents of alkali hydroxide. Accordingly, $H_2[PO_3F]$ and HCl or HBr are formed, as was confirmed by chromatography. $Li[PO_2ClF]$ *(3)* and $Li[PO_2BrF]$ *(4)* were obtained on treatment of ethereal solutions of *(1)* or *(2)*, respectively, with LiBr; they also are hydrolyzed and then require 2 equivalents of NaOH for neutralization.

Doublets appear in the ^{19}F- and ^{31}P-NMR spectra (external standards: CF_3COOH, 85% H_3PO_4) of *(1)* and *(2)* because of FP and PF coupling.

	$H[PO_2ClF]$ *(1)*	$H[PO_2BrF]$ *(2)*
^{19}F-NMR	$\delta = -33.3$ ppm	$\delta = -46.3$ ppm
	$J_{FP} = 1055$ Hz	$J_{FP} = 1106$ Hz
^{31}P-NMR	$\delta = +1.96$ ppm	$\delta = +15.9$ ppm
	$J_{PF} = 1050$ Hz	$J_{PF} = 1103$ Hz

The acids *(1)* and *(2)* scatter so feebly that Raman spectra could not be obtained. Therefore, the IR spectra of the salts *(3)* and *(4)* were measured.

$Li[PO_2ClF]$ *(3)*, Nujol suspension, values in cm^{-1}: 1254 vs $\nu_{as}PO_2$, 1133 vs ν_sPO_2, 876 vs νPF, 630 vs νPCl, (551 vw), 490 w δ, 452 s δ, 381 vs δ, 274 s δ.

$Li[PO_2BrF]$ *(4)*, KBr disk, values in cm^{-1}: 1282 vs $\nu_{as}PO_2$, 1160 vs ν_sPO_2, 874 vs νPF, 558 s, 522 s νPBr(?).

Experimental:

(1): a) $H[PHO_2F]$ (8.4 g, 0.1 mol) is added dropwise to a solution of Cl_2 (10–12 g) in stirred and ice-cooled anhydrous CCl_4 (100 ml). The CCl_4, HCl, and excess of Cl_2 are removed at reduced pressure and the residual oil is fractionated in a high vacuum below 50 °C. *(1)* condenses in a cold trap at −23 °C (solid + liquid CCl_4). After several successive distillations under these conditions the yield amounts to *ca.* 30% (3.5 g).

b) H_2O (18 g, 1 mol) is added dropwise to a solution of $POCl_2F$ (137 g, 1 mol) in anhydrous ether (400 ml) stirred vigorously at −70 °C. After removal of the cooling-bath the mixture is stirred until it reaches room temperature and no further evolution of HCl can be observed. The ether is removed at reduced pressure and the residue is fractionated as in a). The yield is *ca.* 50% (60 g).

(2): Preparation analogous to *(1)* a). CCl_4 100 ml, Br_2 7.5 ml, $H[PHO_2F]$ 8.4 g (0.1 mol). Yield *ca.* 25% (4 g).

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[1] *H. Grunze*, Z. Chem. *3*, 297 (1963); *6*, 266 (1966); *E. J. Schimitschek* and *J. A. Trias*, Inorg. Nucl. Chem. Lett. *6*, 761 (1970).

[2] *A. Simon* and *C. Stölzer*, Chem. Ber. *93*, 1323 (1960).

[3] *H. Falius*, Angew. Chem. *82*, 702 (1970); Angew. Chem. internat. Edit. *9*, 733 (1970).

Molecular Structure of Bis(hexamethylbenzene)-ruthenium(0)[**]

By *Gottfried Huttner*, *Siegfried Lange*, and *Ernst O. Fischer*[*]

As a result of ^1H-NMR investigations *Fischer* and *Elschenbroich* suggested that the diamagnetic bis(hexamethylbenzene)ruthenium(0) has a structure in which the C_6 skeleton is no longer planar[1]. This proposal has been substantially confirmed by the present X-ray structure analysis.

The compound crystallizes in the monoclinic space group $P2_1/c(C_{2h}^5$, No. 14) with cell constants $a = 15.51$, $b = 8.07$, $c = 16.73$ Å, $\beta = 90°$, $V = 2094$ Å^3, $d_{calc} = 1.305$, $d_{exp} = 1.339$ g/cm^3, $Z = 4$.

The analysis is based on a total of 2696 different independent non-zero intensities in the range $0 \leq \sin\vartheta/\lambda \leq 0.65$, which were obtained from two crystals on a Weissenberg diffractometer with monochromated radiation ($Mo_{K\alpha}$, $\lambda = 0.71069$ Å). An empirical absorption correction[2] was applied as well as the usual Lorentz and polarization factor corrections. The structure was determined by conventional Patterson and Fourier methods. Refinement in an anisotropic model led to an agreement factor of $R_1 = 0.043$. All hydrogen atoms were located. Their contributions to the structure factors were included in the calculations.

The geometry of the molecule could roughly be classified by mirror symmetry [C_s; mirror plane through Ru and the centers of bonds C(11)—C(16) and C(21)—C(26)]. However, deviations of some of the individual bond lengths and bond angles from this idealized symmetry are significant (Fig. 1).

One of the rings in the molecule is planar ($\sigma = 0.009$ Å) with a mean C—C distance of 1.410(4) Å. Comparison with the C—C distance in hexamethylbenzene (1.39 Å)[3] seems to indicate strong participation of the antibonding orbitals of the benzene ring in the complex bonding. The distance of the Ru atom from the best plane of the atoms of this ring amounts to 1.75 Å; the projection of the Ru on to this plane lies approximately in the center of the ring.

The second ring is bent about the axis C(12)—C(15). The distance of the Ru from the best plane through atoms C(12), C(13), C(14), and C(15) ($\sigma = 0.009$ Å), amounts to 1.73 Å. This plane makes an angle of 5.2° with that of the planar ring and an angle of 42.8° with the plane defined by C(12),

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[**] We thank the Leibniz-Rechenzentrum der Bayerischen Akademie der Wissenschaften for computer time and the Deutsche Forschungsgemeinschaft for support of this investigation.

C(11), C(16), and C(15) ($\sigma = 0.001$ Å). Similar relations were found for the six-membered ring of π-cyclopentadienyl[hexakis(trifluoromethyl)benzene]rhodium[4]. However, whereas for the latter compound the bending of the benzene nucleus could be ascribed to the influence of the trifluoromethyl groups[5], the present structure shows that the distortion can be caused simply by an excess of two electrons over the noble gas configuration of the central atom. The cyclic conjugation in the ring is thus considerably disturbed (see Fig. 1). The bond length C(16) to C(11) of 1.327(10) Å is that of a pure double bond.

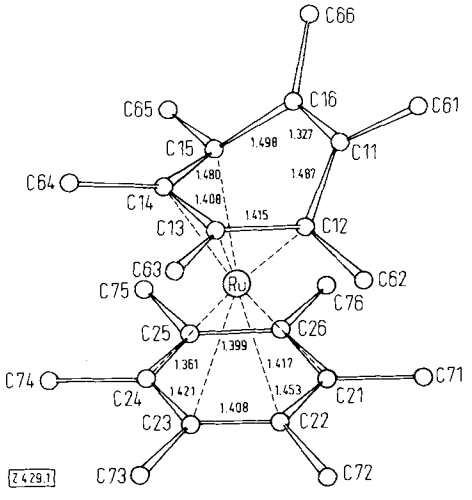


Fig. 1. Molecular structure of bis(hexamethylbenzene)ruthenium(0). None of the standard deviations of the C—C bond lengths in the rings exceeds 0.012 Å.

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German version: Angew. Chem. *83*, 579 (1971)

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[3] *L. O. Brockway* and *J. M. Robertson*, J. Chem. Soc. *1939*, 1324.
[4] *M. R. Churchill* and *R. Mason*, Proc. Roy. Soc. (London) *279*, 61 (1965).
[5] *M. R. Churchill* and *R. Mason*, Proc. Chem. Soc. (London) *1963*, 365.

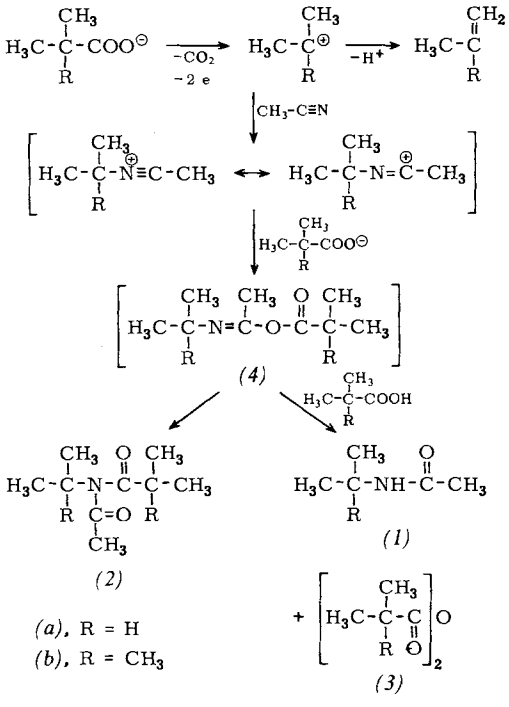
N-Alkylimino Acid Anhydrides as Intermediates in Anodic Oxidation of Aliphatic Carboxylic Acids in Acetonitrile

By *Hans Günter Thomas*[*]

In the anodic oxidation of aliphatic carboxylic acids in acetonitrile[1] products are obtained that are to be ascribed to attack by a carbonium ion on the acetonitrile.

If isobutyric acid is electrolyzed in acetonitrile with carbon electrodes at −10 °C or below, there are formed, besides propene, carbon dioxide, and hydrogen in a total yield of *ca.* 70%, *N*-isopropylacetamide *(1a)*, *N*-acetyl-*N*-isobutyrylisopropylamine *(2a)*, and isobutyric anhydride *(3a)*. Electrolysis of pivalic acid under the same conditions affords, besides isobutene, carbon dioxide, and hydrogen as main products, *N-tert*-butylacetamide *(1b)* and pivalic anhydride *(3b)*.

A first thought is to regard *(1)* as the product of a Ritter reaction; but then the formation of compounds *(2)* and *(3)* cannot be explained. Control experiments excluded the possibility that diacylamines *(2)* could be formed by acylation of *(1)* by *(3)* under the conditions of the electrolysis. Nor can the diacylamines acylate the starting acid



with formation of *(3)*. Rather, a common intermediate must underly the formation of compounds *(1)* to *(3)*. This could be the imino acid anhydride *(4)*, which belongs to a class of compounds which has as yet not been synthesized in the aliphatic series and of which there are so far only cyclic examples[2].

Imino acid anhydrides *(4)* are transformed into diacylamines *(2)* by a known rearrangement reaction[3]; reaction of the imino acid anhydrides with isobutyric acid or pivalic acid affords a straightforward explanation of the formation of the acetamides *(1)* and the anhydrides *(3)* in a ratio 1:1.

The rearrangement product *(2b)* was not found after electrolysis of pivalic acid, perhaps because of steric hindrance at the nitrogen atom.

Although imino acid anhydrides of type *(4)* could not be isolated in the pure state[4], electrolysis at low temperatures provides a method of producing these compounds *in situ* and studying their acylating powers for substances containing OH, NH_2, and SH groups.

Electrolysis of isobutyric acid in acetonitrile:

A solution of isobutyric acid (132 g, 1.5 mol) in anhydrous acetonitrile (2100 ml) containing a little (2 g, 0.02 mol) triethylamine is electrolyzed in a gas-tight circulating apparatus with cylindrical carbon electrodes, at −10 °C, a constant current density of 0.2 A/dm², and 6 to 9 V terminal voltage, until gas chromatography showed that not more than 20% of the isobutyric acid remained unconsumed.

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For working up, the acetonitrile was distilled off through a Vigreux column; the liquid residue (107 g) distills between 25 and 42 °C/0.1 torr without a column. The distillate (90.5 g) obtained consisted of isobutyric acid 23.6%, amide *(1a)* 28.0%, anhydride *(3a)* 40.8%, and diacylamine *(2a)* 7.5%.

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German version: Angew. Chem. *83*, 579 (1971)

[1] *L. Eberson* and *K. Nyberg*, Acta. Chem. Scand. *18*, 1567 (1964); *J. M. Kernprobst, A. Laurent*, and *E. Laurent-Dieuzeide*, Bull. Soc. Chim. Fr. *1968*, 3657.

[2] Lactim esters (*Houben-Weyl-Müller*: Methoden der organischen Chemie. Thieme, Stuttgart 1958, Vol. 11/2, p. 580), azalactones (*Houben-Weyl-Müller*: Methoden der organischen Chemie. Thieme, Stuttgart 1958, Vol. 11/2, p. 372), phthaliminoanhydride.

[3] *O. Mumm, H. Hesse*, and *H. Volquartz*, Ber. dtsch. chem. Ges. *48*, 388 (1915).

[4] However, amidotriazole enol ester was isolated by *H. Bauer et al.* Angew. Chem. *83*, 115 (1971); Angew. Chem. internat. Edit. *10*, 129 (1971).

Experimental Evidence for Kink Formation

By *G. Lagaly* and *Armin Weiss*[*]

In the past years some types of movements in polymers have been interpreted by formation and rearrangements of kinks and jogs[1, 2], *i.e.* special rotational isomers of the hydrocarbon chains containing *gauche* bonds (Fig. 1). The formation of kinks and jogs is mainly concluded from relaxation properties[3–5]. Since by conformational changes from *trans* to *gauche* the length of the alkyl chain decreases by a multiple of 1.27 Å, kink formation should become evident by chain length measurements.

In the systems studied so far (polymers and alkanes) kink formation occurs statistically or in small kink blocks between unaltered alkyl chains. Therefore, hitherto, it has been impossible to measure the decrease in the chain length directly. Now, we have succeeded in demonstrating the shortening of the alkyl chains as a consequence of kink formation by direct X-ray measurements.

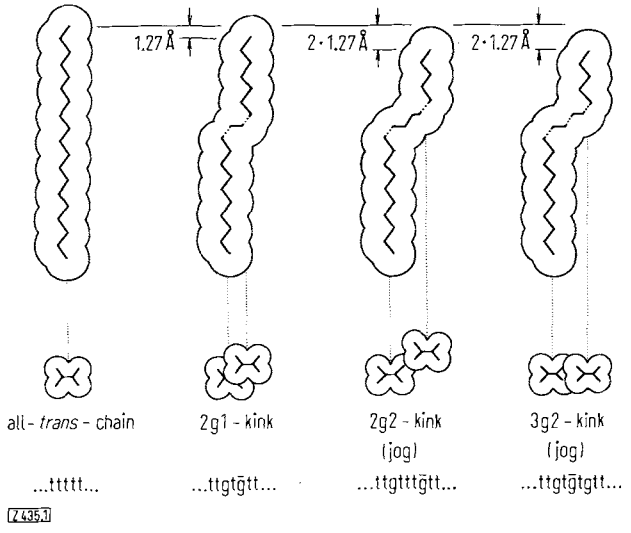


Fig. 1. Some conformations of the alkyl chains with kinks and jogs.

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The *n*-alkanol complexes of *n*-alkylammonium layer silicates[6] were used as models. In these compounds the alkanol molecules and the alkylammonium ions arrange themselves in bimolecular layers between the silicate sheets, with the alkyl chains perpendicular to the silicate layers. Since the distance between the silicate layers (= basal spacing) can be easily measured by X-ray analysis, the thickness of the bimolecular interlayer can be determined with high accuracy and the shortening of the alkyl chains can be directly detected.

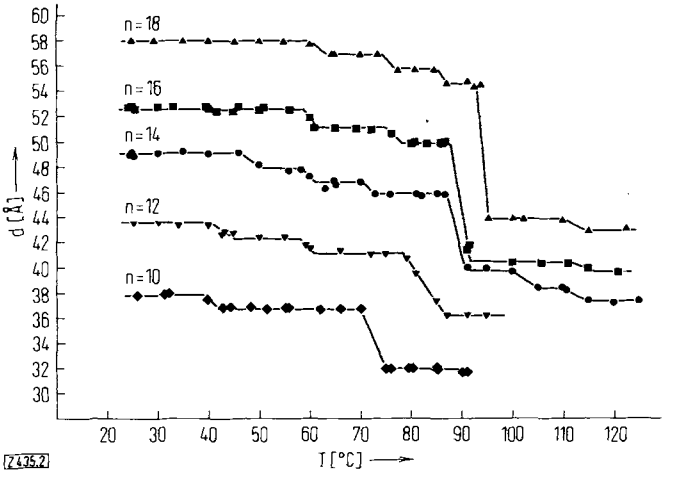


Fig. 2. Variation of the basal spacings *d* of *n*-alkanol complexes of *n*-alkylammonium beidellites with temperature (*n* = number of carbon atoms in the alkanol molecule = number of carbon atoms in the alkylammonium ion).

The basal spacings of the alkanol complexes decrease in regular steps of 1.1—1.3 Å with increasing temperature. Fig. 2 shows, as examples, the basal spacings of the *n*-alkanol complexes of *n*-alkylammonium beidellites. (The chain lengths in the alkanol molecules are equal to the chain lengths in the alkylammonium ions.) The change in the basal spacings with increasing temperature are reproducible and reversible, but hysteresis is often observed. The height of the steps corresponds exactly to the shortening of the alkyl chains as calculated for kink formation.

From these results it can be concluded that simple ("2g1") kinks are introduced in the alkyl chains with increasing temperature. The number of kinks per chain, however, seems to have an upper limit; exceeding this limit, the structure rearranges to a high temperature form with drastically reduced basal spacings. It has to be assumed that this transformation is caused by a rearrangement of simple 2g1 kinks to high order kinks (= jogs). If the temperature is raised still further, additional small steps in the decrease in the basal spacings are observed.

The results reported in this paper indicate that kink formation and kink rearrangements have to be considered in discussions of bimolecular films of long chain alkyl compounds[7].

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German version: Angew. Chem. *83*, 580 (1971)

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[2] *H. Hässler* and *H. J. Bauer*, Kolloid-Z. Z. Polymere *230*, 194 (1969).

[3] *W. Pechhold*, Kolloid-Z. Z. Polymere *228*, 1 (1968).

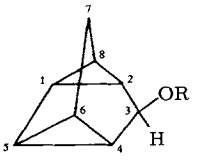
[4] *K. H. Illers*, Kolloid-Z. Z. Polymere *231*, 622 (1969).

[5] *R. Hosemann*, Ber. Bunsenges. Physik. Chem. *74*, 755 (1970).
[6] *G. Lagaly* and *Armin Weiss*, Kolloid-Z. Z. Polymere *216/17*, 356 (1967); *237*, 266, 364 (1970); *238*, 485 (1970); *243*, 48 (1971).
[7] *G. Lagaly* and *Armin Weiss*, Kolloid-Z. Z. Polymere, in press.

An Energy Surface for Acetolysis *via* C_8H_9 Cations from *exo*-Tetracyclo[3.3.0.0^{2,8}.0^{4,6}]oct-3-yl *p*-Nitrobenzoate[**]

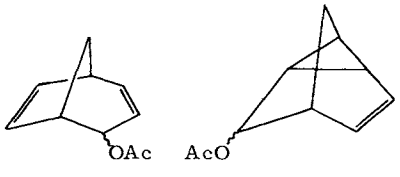
By *Wolfgang Lotsch* and *Andrew S. Kende*[*]

We wish to report equilibration and deuterium labeling studies involving a series of tautomeric C_8H_9 cations derived from *exo*-tetracyclo[3.3.0.0^{2,8}.0^{4,6}]oct-3-yl *p*-nitrobenzoate *(1)*, R = *p*-nitrobenzoyl[1]. These data permit construction of an energy surface relating the three distinct carbon skeletons observed in this rearrangement network.



(1)

Acetolysis of pure *exo-(1)*, R = *p*-nitrobenzoyl, in glacial acetic acid containing an equivalent of sodium acetate gave after 5.5 h reflux a 93% yield of mixed acetates, purified by vacuum distillation at 35 °C. Preparative gas chromatography[2] of the distillate yielded 60% of the mixed epimeric acetates *(2)*, 37% of epimeric tricyclic acetates *(3)*, and *ca.* 3% of unidentified by-product different from either *exo-* or *endo-(1)*, R = acetyl; the presence of more than 0.1% of either of the latter could have been detected.



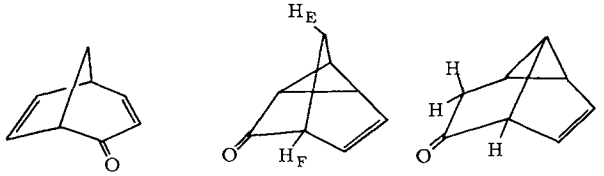
(2) *(3)*

The mixture of bicyclic acetates *(2)* (69% *exo* and 31% *endo*)[3] was saponified and oxidized by chromium trioxide-pyridine complex in methylene chloride[4] to an unsaturated ketone *(4)*, $\nu_{max}^{CCl_4}$ 1690 cm^{-1}, parent *m/e* = 120, identified by IR and NMR comparison with authentic bicyclo[3.2.1]octa-3,6-dien-2-one[5]. In a similar manner, the tricyclic acetates *(3)* (59% *exo* and 41% *endo*)[6] were oxidized to a ketone *(5)*, $\nu_{max}^{CCl_4}$ 1740 cm^{-1}, *m/e* = 120. This ketone was distinguished from the isomeric alternative *(6)* by 90-MHz decoupling studies which, *inter alia*, clearly demonstrated the 6-Hz vicinal coupling between bridgehead proton H_F and one of the bridge protons, H_E.

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[**] A. S. K. makes acknowledgment to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The award of a Deutscher Akademischer Austauschdienst Fellowship to W. L. is gratefully acknowledged.

Gas chromatographic analysis of acetate composition as a function of solvolysis time revealed that the kinetic acetolysis products of *(1)* are the unrearranged acetates *exo-(1)*, R = Ac, and *endo-(1)*, R = Ac[7], but that the



(4) *(5)* *(6)*

percentage of tricyclic acetates *(3)*, and then of bicyclic acetates *(2)*, gradually increases as secondary equilibration of acetates occurs. The 5.5-h mixture is the equilibrium mixture which can be independently reached starting with a sample of *exo-(1)*, R = Ac (Table 1).

Table 1. Composition of acetates from *exo-(1)*, R = *p*-nitrobenzoyl or *exo-(1)*, R = Ac.

Starting material	Reaction time (h)	*exo-(1)*, R = Ac (%)	*endo-(1)*, R = Ac (%)	*(2)* (%)	*(3)* (%)
exo-(1), R = *p*-nitrobenzoyl	0.17	30	46	13	11
	1.00	9	16	43	32
	2.00	4	4	54	38
exo-(1), R = Ac	1.00	15	15	39	31
	2.00	5	5	53	37

The mechanism leading from *(1)* to systems *(3)* and *(2)* is further delineated by the fate of deuterated *exo-(1)*, R = *p*-nitrobenzoyl[8], on solvolytic rearrangement. The isolation and oxidation sequence described above converts the latter to the corresponding deuterated rearrangement ketones [D$_1$]-*(5)* and [D$_1$]-*(4)* which are labeled specifically (Figure 1).

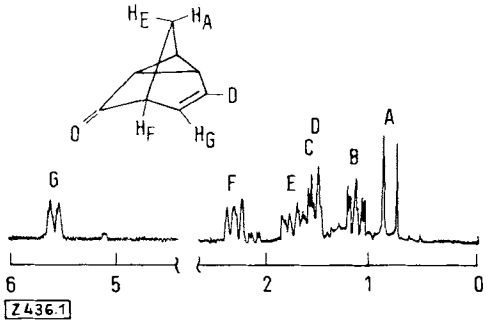


Fig. 1. NMR spectrum of [D$_1$]-*(5)* in C_6D_6 solution, measured in ppm relative to internal $(CH_3)_4Si$ (not shown) at 90 MHz.

These data implicate stepwise, stereospecific cleavage of first one, then the second cyclopropane ring to yield ultimately the allylic cation of the bicyclic series[9]. Moreover, the labeling pattern unambiguously excludes any degeneracy arising from equilibration of the C_3, C_2, and C_1 bridges in the bicyclic cation despite the availability of simple 1,2-shifts which would achieve that result.

If our equilibration results are taken in conjunction with the recent kinetic data obtained by *Diaz*, *Sakai*, and *Winstein*[7] an approximate energy diagram for the isomerizations observed in this C_8H_9 network may be con-

structed (Figure 2). For simplicity only the solvolyses of the *exo* isomers of the *p*-nitrobenzoates are indicated (heavy lines); the isomerization steps are shown by the dashed lines connecting the three carbonium ions. The

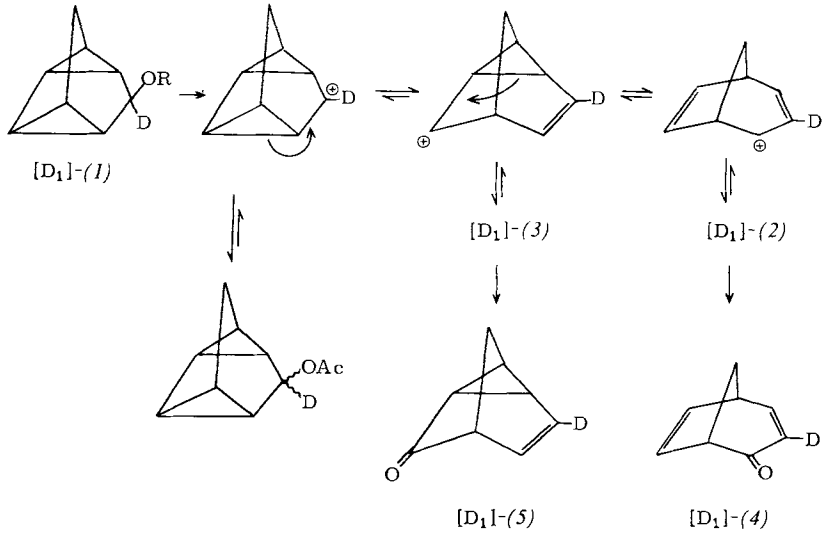


diagram assumes a typical[10] frequency factor A of $10^{11}\ s^{-1}$ for the solvolyses, a local minimum of *ca.* 5 kcal $mole^{-1}$ for each cation relative to the solvolysis transition state, and an equilibrium concentration of *exo-(1)*, R = Ac, of 0.01%.

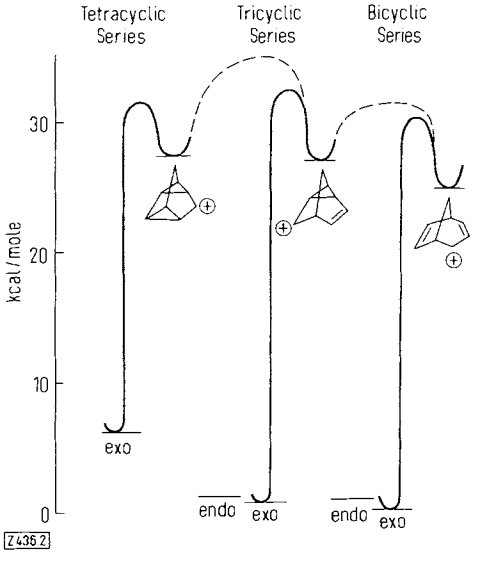


Fig. 2. Diagram depicting ΔH for reaction pathways relating tetracyclic, tricyclic, and bicyclic *p*-nitrobenzoates and the corresponding carbonium ions from solvolysis.

All of the data are consistent with equilibration *via* at least three distinct carbonium ions; there is no evidence for a single common intermediate having the bishomocyclopentadienyl cation structure.

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German version: Angew. Chem. *83*, 581 (1971)

[1] Synthesis of this compound, m. p. 132.5—133 °C, was carried out by treatment of the pure *exo* alcohol [*N. A. LeBel* and *R. W. Liesemer*, J. Amer. Chem. Soc. *87*, 4301 (1965)] with *p*-nitrobenzoyl chloride in pyridine.

[2] Gas chromatographic separation was carried out using a 4.5-ft SE-30 column, 0.25 inch in diameter, at 103 °C.

[3] Isomer ratio is based on integration of the δ 3.75 proton (*exo* alcohol C*H*OH) *vs.* the δ 4.18 proton (*endo* alcohol C*H*OH).

[4] *R. Ratcliffe* and *R. Rodehorst*, J. Org. Chem. *35*, 400 (1970).

[5] Prepared by Mr. *R. G. Eilerman* of this laboratory according to the procedure of *P. K. Freeman* and *D. G. Kuper*, Chem. Ind. (London) *1965*, 424.

[6] Isomer ratio is based on integration of the δ 4.25 proton (*exo* alcohol C*H*OH) *vs.* the δ 4.85 proton (*endo* alcohol C*H*OH). We are indebted to Prof. *J. M. Nickolson* (Howard University, Washington, D. C., USA) for unpublished NMR data in this series.

[7] Our results are thus in accord with the reported formation of 99% unrearranged alcohols (35% *exo*, 64% *endo*) from *(1)* in aqueous acetone under apparent kinetic control: *A. F. Diaz*, *M. Sakai*, and *S. Winstein*, J. Amer. Chem. Soc. *92*, 7477 (1970).

[8] This deuterated ester was prepared by $LiAlD_4$ reduction of the tetracyclic ketone, followed by esterification as described in reference [1]. The ester gave a satisfactory NMR spectrum and combustion analysis.

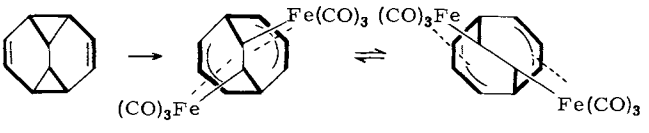
[9] Cf. the rearrangement of the related tetracycloheptyl system: *P. R. Story* and *S. R. Fahrenholtz*, J. Amer. Chem. Soc. *88*, 374 (1966).

[10] This value was extrapolated from the parameters tabulated by *R. C. Fort, Jr.* and *P. von R. Schleyer*, Advan. Alicyclic Chem. *1*, 284 (1966).

Diferratricyclododecatriene: An Iron Heterocycle Showing Rapid Degenerate Valence Isomerization[1]

By *Rudolf Aumann*[*]

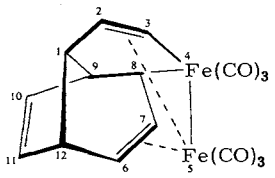
We recently described the autogenous intramolecular rearrangement *(1a)*⇌*(1b)* of diferratetracyclododecadiene[2].



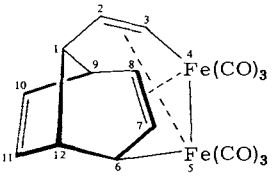
We now report the rapid degenerate valence isomerization of the iron heterocycle, $C_{10}H_{10}Fe_2(CO)_6$ *(2)*, m. p. 89 °C, which is isomeric with *(1)*. 4,4,4,5,5,5-Hexacarbonyl-4,5-diferratricyclo[7.3.0.0^{6,12}]dodeca-2,7,10-triene *(2)* is form-

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ed in 10% yield when $Fe_2(CO)_9$ reacts with bullvalene[3,4]. Its composition follows from the mass spectrum and elemental analysis.



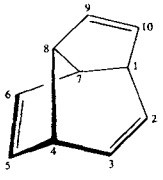
(2a)



(2b)

The CH skeleton was determined from the coupling pattern observed on NMR analysis. The geometry of the uncomplexed part of the molecule differs only slightly from that of tricyclo[5.3.0.0^{4,8}]deca-3,7,9-triene *(3)*[5], as shown by a comparison of the NMR coupling constants of *(2)* and *(3)*:

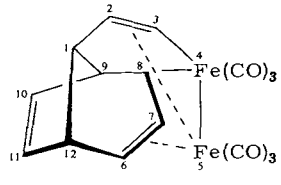
(2): $J_{9,10}=2.5$; $J_{10,11}=5.9$; $J_{11,12}=2.5$ Hz
(3) [5]: $J_{6,7}=2.0$; $J_{5,6}=5.9$; $J_{4,5}=3.0$ Hz



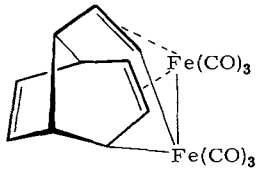
The CH skeleton of *(2)* is characterized by the observed long-range couplings: $J_{7,9}\approx J_{7,12}\approx 1.3$; $J_{1,6}\approx J_{1,8}\approx 1.5$; $J_{6,8}=2.0$; $J_{1,10}=J_{1,11}=0$ Hz[6]. $J_{13_{C(3)-H(3)}}$ indicates sp^2 hybridization of C-3. The vicinal coupling $J_{2,3}=9.5$ Hz accords with assumption of a strain-free, complexed double bond between C-2 and C-3[7,13].

The Mössbauer spectrum[8] of *(2)* shows different *s*-electron densities at the nuclear sites of the two iron atoms ($IS_{FeA}=0.13_0\pm0.01$; $IS_{FeB}=0.24_6\pm0.01$ mm/s) and different field gradients ($QS_{FeA}=0.90\pm0.01$; $QS_{FeB}=1.14\pm0.01$ mm/s).

Since the IR spectrum does not indicate any bridging carbonyl group, we suggest structures *(2a)* and *(2b)* for *(2)*. Formulation as *(2a)* is favored in view of the Mössbauer measurements, but it must be emphasized that *(2a)* and *(2b)* are approximations so far as the method of writing the valence bonds is concerned. Both *(2a)* and *(2b)* have pendants in the ferracyclopentadiene and ferracyclohexadiene complexes, where comparable bonding relations have been proved by X-ray structure analyses[9].



A



B

The dynamic NMR spectra of *(2)* reproduced in Fig. 1 result from rapid simultaneous exchange in magnetic surroundings between the proton pairs H(10)/H(11), H(9)/H(12), and H(6)/H(8), which can occur only by mutual rearrangement of the enantiomers A and B. As expected, in this process the signals assigned to the protons H(1), H(2), H(3), and H(7) remain largely unchanged.

The NMR signals of H(10) and H(11) coalesce when the temperature is raised (Fig. 1). Since coalescence of the signals from H(9) and H(12), and from H(6) and H(8), is

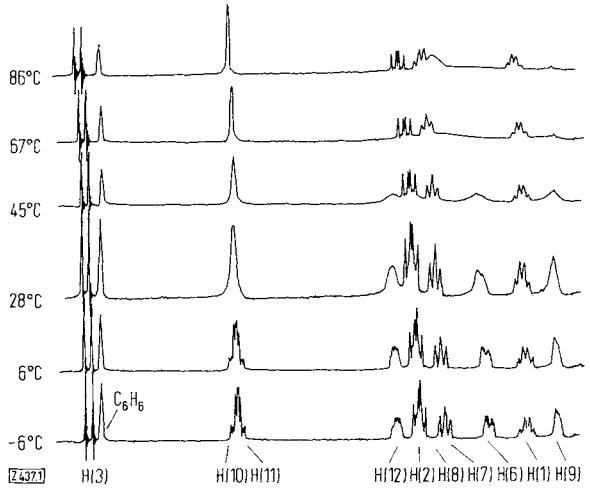


Fig. 1. The dynamic NMR spectra of *(2)* (10% solution in C_6D_6, 100 MHz).

to be expected only above the decomposition temperature of *(2)*, exchange of the magnetic surroundings of these proton pairs was demonstrated (Fig. 2) by the double resonance relaxation method developed by *Forsén* and *Hoffman*[10].

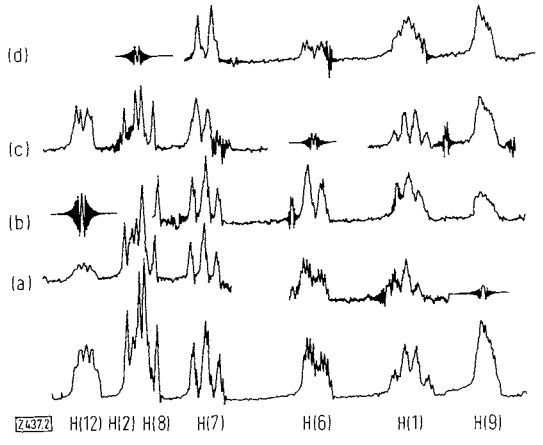


Fig. 2. Double resonance relaxation experiments with the proton pairs H(9)/H(12) (a, b) and H(6)/H(8) (c, d) of *(2)* (metastable C_6D_6 solution at −6°C; 100 MHz).

As can be seen from Fig. 2(a), "saturation" of H(9) by a strong electromagnetic field leads to a decrease in intensity ("partial saturation") of the signal of the proton H(12) that "exchanges" with H(9). Contrariwise, a decrease in the intensity of the H(9) signal is achieved by "saturation" of H(12) [Fig. 2(b)]. Similar effects can be demonstrated for the proton pair H(6)/H(8) [Fig. 2(c) and (d)]. The decrease in intensity is due to an equilibrium whose position is determined by the rate of exchange and the spin-lattice relaxation[10]. The following Eyring parameters for racemization of *(2)* have been calculated from quantitative measurements of the establishment of equilibrium[11] be-

tween the proton pair H(9)/H(12) between $-12.5°$ and $+12.0°C$:

$\Delta H^{\neq} = 10.4 \pm 1$ kcal mol^{-1}
$\Delta S^{\neq} = -18.5 \pm 3$ kcal deg^{-1} mol^{-1}
$\Delta G^{\neq} = 16.2$ kcal mol^{-1} [12]

(2) can be considered as a model compound showing each geometric step in the transfer of a vinyl group from one metal to another.

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[1] Part 5 of transition-metal complexes of $(CH)_n$ compounds. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 4: *R. Aumann*, Angew. Chem. *83*, 177 (1971); Angew. Chem. internat. Edit. 10, 190 (1971).

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[4] The skeletal rearrangement leading to this compound will be discussed elsewhere.

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[6] Absolute coupling constants.

[7] $J = 9.0$ Hz for diferracyclohexadienethione, $C_4H_4SFe_2(CO)_6$ (*R. Aumann*, unpublished work).

[8] I thank Dr. *B. Hentschel*, Münster, for measurement of the Mössbauer spectrum.

[9] Cf. *A. A. Hock* and *O. S. Mills*, Proc. Chem. Soc. *1958*, 223; Acta Crystallogr. *14*, 139 (1961); *E. Weiss*, *W. Hübel*, and *R. Merenyi*, Chem. Ber. *95*, 1155 (1962); *M. van Meerssche*, *P. Piret*, *J. Meunier-Piret*, and *Y. Degreve*, Bull. Soc. chim. Belges *73*, 824 (1964).

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[11] Since our NMR spectrometer is fitted with a field-frequency lock system, we, unlike *Forsén* and *Hoffman*, determined the intensity change of the H(12) signal on saturation of H(9) by measurements in the HA mode, using an XY register with automatic paper supply externally to the spectrometer.

[12] Independently of this measurement, $\Delta G^{\neq} = 16.0$ kcal mol^{-1} was determined from the coalescence temperature of the signals of the proton pair H(10)/H(11).

[13] The chemical shifts and coupling constants of the vinyl protons are in agreement with values observed for $C_2H_3Fe_2(CO)_6SR$ by *R. B. King*, *P. M. Treichel*, and *F. G. A. Stone*, J. Amer. Chem. Soc. *83*, 3600 (1961).

Desorption Spectra in the Adsorption System Iron/Nitrogen[1]

By *Gerd Wedler* and *Dieter Borgmann*[*]

Discussion of the mechanism of ammonia synthesis on iron catalysts has been generalized again by the recent work of *Brill*, *Ruch et al.*[2–4], and *Schmidt*[5], so that particular interest attaches to studies of the adsorption state of the nitrogen on very pure iron surfaces such as can be obtained by evaporation under ultra-high vacuum. The adsorption states in such systems can be characterized by measuring the surface potential and the desorption spectra, *i.e.* the temperature-dependence of the desorption[6]. The latter is obtained by loading the adsorbent with gases at a low temperature and then recording the changes in pressure above the adsorbent with change in temperature when the adsorption system is heated with continuous pumping off of the gases. The adsorbate is desorbed at lower or higher temperature according to the strength of its binding to the adsorbent, and this desorption can be recognized by a temporary pressure maximum. The desorbed gas can also be analyzed qualitatively by using a quadrupole mass spectrometer[7] in place of an ionization gauge for measuring the pressure.

Figure 1 shows the desorption spectrum of nitrogen that had been adsorbed at 77 °K on a *ca.* 90 Å-thick iron film that was obtained by evaporation at $77\,°K/2 \cdot 10^{-10}$ torr

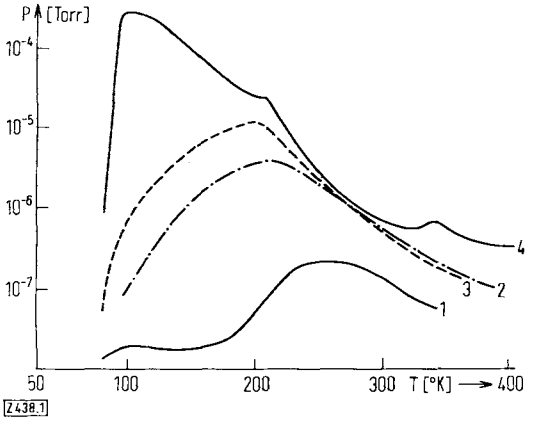


Fig. 1. Desorption spectra in the system iron/nitrogen. Curve 1, $\Theta = 0.013$; curve 2, $\Theta = 0.024$; curve 3, $\Theta = 0.05$; curve 4, $\Theta = 0.5$.

and annealed at 400 °K. The nitrogen was prepared within the apparatus by thermal decomposition of degassed sodium azide; mass-spectrometric analysis did not disclose any impurity in it. The coverage Θ is used as parameter in Fig. 1; it is referred to the monomolecular coverage ($\Theta = 1$), which in the adsorption system iron/nitrogen at 77 °K can be reached only at an equilibrium pressure of $P > 10^{-4}$ torr and corresponds to $7.5 \cdot 10^{14}$ molecules of N_2 per cm^2.

If the iron film is covered with nitrogen only up to $\Theta = 0.013$ (curve 1), desorption sets in above 170 °K and a desorption maximum is observed at 265 °K. This maximum shifts to lower temperatures (200 °K) as the coverage is increased (curve 2, $\Theta = 0.024$; curve 3, $\Theta = 0.05$), indicating that for the adsorption state characterized by this maximum the strength of bonding between the adsorbent and the adsorbate decreases with increasing coverage.

A shoulder is evident on the left side of the desorption maximum curve, even at $\Theta = 0.05$, and this must be ascribed to a second adsorption state of the nitrogen. This state becomes predominant on further increase of the coverage: at $\Theta = 0.5$ (curve 4) its desorption maximum is very highly developed immediately above 77 °K, while the species desorbing at 200—265 °K is then evident only as a shoulder.

At $\Theta > 0.1$, besides these two adsorption states, a third is observed that shows a desorption maximum at 330 °K (curve 4). Although we are here concerned with a state involving the strongest bonding between the adsorbate and the adsorbent, it is formed in detectable amount only at the higher coverages.

It follows from the height of the pressure increase that the number of molecules characterized by the desorption maximum between 77° and 90 °K greatly exceeds that of those in other states. The reversible adsorption occurring at 77 °K and $\Theta > 0.5$ also leads to this state, shifting the desorption maximum to still lower temperatures. This species of adsorbed nitrogen is positively polarized, as is shown by the decrease of the work function of the iron[8] on adsorption.

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The state with desorption maximum between 200° and 265 °K is the only one occurring at $\Theta < 0.05$. It follows from the constancy of the height of the maximum that its amount is not further increased by increase of the coverage. It can amount to, at most, 5% of the total amount bound to the iron surface. *Richter*[8] has shown that this species makes the work function of the iron film increase, whence it follows that nitrogen present in this state is negatively polarized.

Still smaller must be the amount of the state that occurs first at $\Theta = 0.1$ and has its maximum at 330 °K, this being shown by the height of its pressure maximum. It can be formed at only very few sites on the surface, and even the smallest quantity of impurity prevents its appearance. The fact that this, the most firmly bound, state appears only at relatively high coverages shows that its formation involves an activation process. *Tompkins et al.* have made similar observations for adsorption of nitrogen on other body-centered cubic metals such as titanium and molybdenum[9] or tungsten[10].

It is certain that the molecular, physically adsorbed nitrogen with the desorption maximum at 77—90 °K does not play a decisive role in ammonia synthesis; and, as the species with a desorption maximum at 330 °K can no longer be observed in presence of even traces of impurity, it seems that the species most interesting for investigation of the ammonia synthesis should be the nitrogen that is desorbed between 200° and 275 °K.

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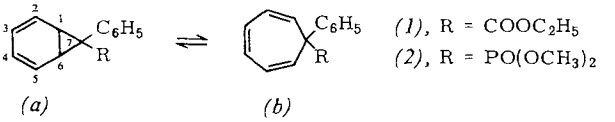
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Two New Norcaradiene-Cycloheptatriene Equilibria[**]

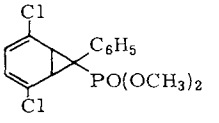
By *Harald Günther, Budi D. Tunggal, Manfred Regitz, Hans Scherer, and Toni Keller*[*]

We recently reported characteristic ^{13}C-NMR data for norcaradienes and cycloheptatrienes[1]. By further ^{13}C- and ^1H-NMR measurements it has now been shown that ethyl 7-phenylcycloheptatriene-7-carboxylate *(1b)*[2] and dimethyl 7-phenylcycloheptatriene-7-phosphonate *(2b)*[3] exist in valence-tautomeric equilibrium with the corresponding norcaradiene forms *(1a)* and *(2a)*, respectively, whereas dimethyl 2,5-dichloro-7-phenylnorcaradiene-7-phosphonate *(3)* exists, within the accuracy of our measurements, solely as the bicycle[4].

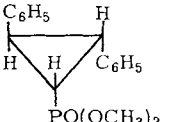


(a) ⇌ *(b)*

(1), R = $COOC_2H_5$
(2), R = $PO(OCH_3)_2$



(3)



(4)

Fourier transform ^{13}C-measurements showed that the resonances for C(1) and C(6) in *(1)* and *(2)* are found clearly at higher field than those for the α-C atoms of cycloheptatriene[1]. They are, however, appreciably deshielded with reference to the corresponding carbon resonances in the norcaradiene system[1] (see Table 1). The unusual position of these resonances must thus be a manifestation of a reversible equilibrium of type *(a)* ⇌ *(b)* where rapid exchange leads to an average value.

Table 1. NMR data of compounds *(1)* to *(3)* for C(1), C(6) and H(1), H(6).

	Temp. (°C)	$\delta_{TMS}(^{13}C)$ (ppm)		Temp. (°C)	$\delta_{TMS}(^1H)$ (ppm)		$K\ (=p_a/p_b)$	$\Delta H^0\ (=H_b^0-H_a^0)$ (kcal/mol)	$\Delta S^0\ (=S_b^0-S_a^0)$ (cal/deg·mol)
(1)	*ca.* 25	85.4	(CCl_4)	+ 30	4.78	(CS_2)	0.42	1.26	5.8
				− 81	4.01	(CS_2)	1.49		
	+17	87.3	(CS_2)	−110	2.99	(CS_2)	—		
	− 3	84.2	(CS_2)						
	−13	82.8	(CS_2)						
(2)	*ca.* 25	58.0	(CCl_4)	− 34	3.42	(CS_2)	3.78	1.21	2.4
				− 99	3.11	(CS_2)	9.95		
				−116	2.87	(CS_2)	—		
(3)	*ca.* 25	36.9	(CCl_4)	*ca.* 25	3.17	(CCl_4)	—	—	—
					$J_{1,6}=9.05$ Hz [a]				
					$J_{3,4}=6.98$ Hz [a]				

[a] Determined by use of the ^{13}C satellites.

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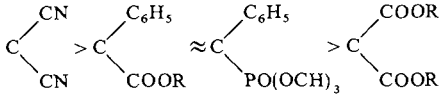
[**] Part 2 of Applications of ^{13}C Resonance Spectroscopy.—Part 1: see [1]. Presented at the 161st Meeting of the American Chemical Society, Los Angeles, March 28 to April 2, 1971.

This interpretation is confirmed by the temperature-dependence of the ^{1}H-NMR spectra of *(1)* and *(2)* (Table 1). After line broadening and signal splitting, the spectra of the norcaradienes *(1a)* and *(2a)* are observed on cooling to −120 °C. The cycloheptatrienes *(1b)* and *(2b)* could not be observed directly so far, apparently because of their low concentration and the overlapping of their resonance signals with those of the norcaradienes. The dynamic process is also indicated for *(1)* by the temperature-dependent ^{13}C resonance signals for C(1) and C(6); here we were able to establish a diamagnetic shift (Table 1) and signal broadening on decrease of the temperature.

To estimate the equilibrium constants K for *(1a)*⇌*(1b)* and *(2a)*⇌*(2b)* we have determined the resonance frequencies of the α-protons in the triene forms by means of model compounds. In 7-monosubstituted cycloheptatrienes replacing isopropyl by C_6H_5, $COOC_2H_5$, or $PO(C_6H_5)_2$ causes deshieldings of 0.18, 0.21, and 0.18 ppm for these protons[5, 6]. If the substituent effects are considered as additive, one obtains $\delta_{1,6}=5.53$ and 5.50 ppm for *(1b)* and *(2b)*, respectively. Using these data, K values were determined from the temperature-dependence of the α-proton resonance between 30° and −100 °C, on the assumption that, of the norcaradienes with different configurations at C(7) (phenyl *endo* or *exo*), one form is dominant in both cases; then, by *van't Hoff*'s method, these K values led to the thermodynamic data for the equilibria listed in Table 1.

Compound *(3)* is shown to be a norcaradiene by both the ^{13}C- and the ^{1}H-NMR data (Table 1). The large vicinal coupling constant $J_{1,6}$ is particularly characteristic of this. With the help of the model compound *(4)*[5] it was further possible to clarify the configuration at C(7) in *(2a)* and *(3)*, since we were able to determine unambiguously the extent of *cis*- and *trans*-coupling between the proton and the phosphorus nucleus on the three-membered ring. For $^3J_{H,P}(cis)$ and $^3J_{H,P}(trans)$ in *(4)* we found values of 16.91 and 1.58 Hz, respectively. Since the H,P coupling in *(2a)* and *(3)* amounts to 17.0 and 16.2, respectively, the phenyl group occupies the *endo*-position in both systems.

The ability of substituents on C(7) to stabilize a norcaradiene[6, 7] is found, on the basis of these and other[8] observations, to be in the order:



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[4] Temperature-dependence of the α-proton resonance of *(1)* was first observed by *Ciganek* (*E. Ciganek*, personal communication); in addition *Hall* and *Roberts* derived the existence of a fluxional system for *(1)* and the corresponding *p*-nitro and *p*-methoxy compounds from the variable ^{1}H-NMR parameters in the region of rapid exchange (*J. D. Roberts*, personal communication).

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Production of F Atoms, H Atoms, and OF Radicals

By *Heinz Gg. Wagner, Jürgen Warnatz*, and *Cornelius Zetzsch*[*]

When studying the rate of reactions of fluorine atoms it is generally necessary to ensure the presence of no—or very little—F_2 in the reaction mixtures, since F_2 in particular generally reacts very rapidly too. Hitherto F atoms have been obtained for such measurements either by microwave discharge in mixtures of CF_4 and He or by titration of NF_2 with N atoms[1]. Reports[2, 3] have already appeared, but without quantitative data, on the production of F atoms from F_2 in microwave discharges. Our own experiments gave at first poor yields of F and relatively high residual concentrations of F_2; appreciably better yields are obtained only if dry fluorine free from HF is used.

Production of F atoms

When a mixture of He and a few parts per thousand of fluorine, purified by freezing out HF and H_2O by liquid nitrogen, is allowed to stream through an electrodeless microwave discharge, the F_2 is almost completely dissociated. At a pressure of 3.5 torr, a flow velocity of 17 m/sec and 100-watt discharge energy the fluorine is consumed to a residue of about 1%. These data refer to the apparatus described in Ref. [1]. The F atoms thus obtained are very well suited for study of reactions of F atoms, since hardly any interfering substance remains present with them.

Production of H atoms

If the mixture of He and F atoms is titrated with H_2 to disappearance of the F atoms, the very rapid reaction leads to a mixture of He, HF, and H atoms with a very low content (*ca.* 1%) of H_2. When small concentrations of H atoms suffice, this process can have advantage over the direct production of H atoms from H_2 in a discharge where an appreciable proportion of the H_2 does not dissociate.

Production of OF

The radical OF has not previously been observed directly in the gas phase, although it is known in a N_2 matrix[4].

If F atoms, produced as above, are mixed with ozone, it is observed that the O_3 is totally consumed at F atom excess. In agreement with *Schumacher*'s results[5], the stable product is O_2. F atoms are consumed in the reaction and reformed during further reaction. OF occurs as intermediate and is later consumed. Since no other O—F compound could be observed with the same concentration profile, it is very unlikely that the mass peak of the OF ion at $m/e=35$ arises by fragmentation of another O—F compound. From these results it can be concluded that, analogously to the reactions of Cl, Br, and I with O_3, the following reaction occurs[6–8]:

$$F + O_3 \rightarrow OF + O_2$$

The rate constant at room temperature is found to be

$$k \approx 5 \cdot 10^{12}\ \mathrm{cm^3\ mol^{-1}\ s^{-1}}$$

Subsequent reactions of OF in this system, which will be reported later, are slow enough to permit the study of their reactions with other compounds. Under the above

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mentioned conditions the concentration of OF amounts to *ca.* 10^{-11} mol cm^{-3}.

The same results for the reaction with O_3 are obtained by using F atoms produced in a microwave discharge in a mixture of CF_4 and He. However, when the F atoms are produced by reaction of NF_2 with an excess of N atoms, the maximal concentration of OF is very much lower, as also is the consumption of F atoms at the beginning of the reaction. It can be assumed that OF is here consumed by the rapid subsequent reaction:

$$N + OF \rightarrow NO + F$$

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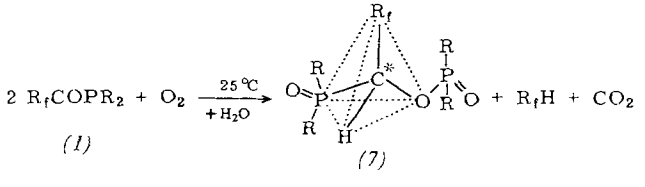
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New Type of Reaction Resulting from the Action of O_2 on Diarylperfluoroacylphosphanes[**]

By *Ekkehard Lindner* and *Hans-Dieter Ebert*[*]

We recently reported the unusual result of oxidizing diphenyl(trifluoroacetyl)phosphane[1,2], which reacts with molecular oxygen to afford racemic 1-(diphenylphosphoryl)-2,2,2-trifluoroethyl diphenylphosphinate. Further work has shown that the formation of the ester is due to a new type of reaction that occurs generally when a perfluoroacyl and two aryl groups are bonded in the phosphane used [cf. *(1)*].



(1) *(7)*

(7a), R = C_6H_5, $R_f = CF_3$ *(7d)*, R = C_6D_5, $R_f = CF_3$ [3]
(7b), R = C_6H_5, $R_f = C_2F_5$ *(7e)*, R = p-$CH_3C_6H_4$, $R_f = CF_3$
(7c), R = C_6H_5, $R_f = C_3F_7$

A prerequisite for this course of the reaction is the presence of a small amount of H_2O, which affords the H atom on the center of chirality; on the other hand, the solvent is only of subordinate importance since the same products are formed in similar yields (*ca.* 25%) in benzene, toluene, cyclohexane, hexane, and even C_6D_6 or dodecafluorocyclohexane. The compositions and structures of the new 1-(diarylphosphoryl)1*H*-perfluoroalkyl diarylphosphinates *(7a)* to *(7e)* follow from elemental analyses, mass, ^1H-, ^{19}F-, ^{31}P-NMR, IR, and Raman spectroscopic studies. The coupling scheme in the high-resolution ^1H-NMR spectrum is characteristic for the proton on the asymmetric C atom (C*), and the two ^{31}P signals indicate two phosphorus atoms in different chemical environments (Table 1). In the IR spectrum the band for $\nu(C{-}H_{aliphat.})$ absorbs at *ca.* 2925 cm^{-1} (solid; KBr).

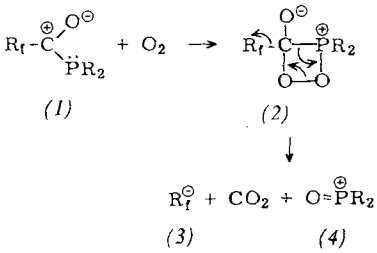
Table 1. Parameters of the ^1H- and ^{31}P-NMR spectra of compounds *(7a)* to *(7c)* (TMS or H_3PO_4 as standard).

Compound	Nucleus	Coupling constant [Hz]	δ (ppm)	Measured at [MHz]
(7a) in [D_6]-Acetone	^1H	$^2J_{HP} = 12.5$ $^3J_{HP} = 4.7$ $^3J_{HF} = 7.8$	− 6.128	90
(7a) in [D_3]-Nitromethane	^{31}P		−23.170 −36.670	30
(7b) in [D_3]-Nitromethane with [D_6]-DMSO	^1H	$^2J_{HP} = 12$ $^3J_{HP} = 6$ $^3J_{HF} = 12$	− 6.2	60
(7b) in CH_3CN	^{31}P		−22.7 −35.2	36.43
(7c) in [D_3]-Nitromethane with [D_6]-DMSO	^1H	$^2J_{HP} = 12$ $^3J_{HP} = 4.5$ $^3J_{HF} = 12$	− 6.23	60

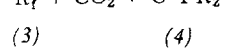
The corresponding alkali diarylphosphinates and fluorinated alcohols are formed on alkaline hydrolysis of *(7a)* to *(7e)*:

$$(OPR_2)_2OCHR_f + 2\,HO^- \longrightarrow 2\,R_2P(O)O^- + R_fCH_2OH$$

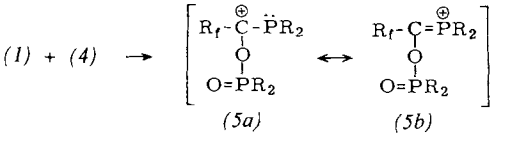
On the basis of these results we suggest the follow course for the formation of compounds *(7)*[4]: In the first step, O_2 adds to *(1)*; a transition state is assumed to consist of



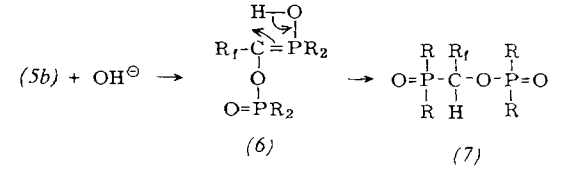
(1) *(2)*



(3) *(4)*



(5a) *(5b)*



(6) *(7)*

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(2), which decomposes into *(3)*, *(4)*, and CO_2; a similar mechanism has been formulated for the oxidation of alkylidenephosphoranes[5]. The ions *(3)* and *(4)* do not combine. We assume rather that *(4)* attacks a second molecule of the starting material *(1)*, while the R_f^- ion *(3)* reacts with H_2O to yield R_fH and HO^-. The HO^- then clearly adds to the cation *(5b)*, forming *(6)*. In a final step, *(6)* stabilizes itself to the ester *(7)*. The stable by-products CO_2 and 1*H*-perfluoroalkane (R_fH) were unambiguously identified in all cases.

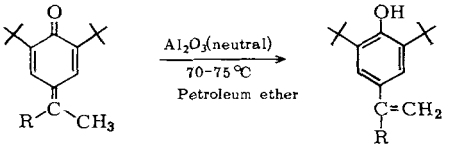
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Isomerization of Quinone Methides to Alkenylphenols[**]

By *Dietrich Braun* and *Bertold Meier*[*]

During our studies of oxygen polyradicals[1] we have found a new synthesis of sterically hindered polymerizable phenol derivatives by isomerization of the stable 2,6-di-*tert*-butylbenzoquinone methides *(1)* to the corresponding alkenylphenols *(2)*.



(1) *(2)*

┼ = tert-Butyl; R = H, CH_3, Phenyl

The isomerization occurs extremely rapidly and quantitatively on use of neutral aluminum oxide. Use of acid aluminum oxide is possible but leads to yields of only 50—60% because part of the isomeric compounds are bound to the catalyst as carbonium ions or react further by oligomerization. Basic aluminum oxide is not suitable because sterically hindered phenols are oxidized in a basic medium by atmospheric oxygen, yielding oily products when the reaction mixture is worked up. It is also impossible to isolate the alkenylphenols if the aluminum oxide is replaced by traces of protic or Lewis acids. This method of isomerization is superior to the classical processes (dehydration of carbinols or decarboxylation of substituted cinnamic acids)[1] because the alkenylphenols are immediately provided in a very pure state.

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Experimental

2,6-Di-*tert*-butylbenzoquinone 4-dimethylmethide[2] (1 g, 0.00406 mol), anhydrous neutral aluminum oxide (1 to 2 g), and light petroleum (15 ml; b.p. 50—70 °C) are heated and stirred magnetically under nitrogen (gas stream) in a round-bottomed flask, fitted with a reflux condenser, in an oil-bath (70—80 °C). The deep yellow color disappears at once. The reaction is complete in 5—15 min. After cooling, the mixture is placed together with the aluminum oxide on a silica gel column and eluted with anhydrous light petroleum (50 ml). Removal of the solvent affords 2,6-di-*tert*-butyl-4-isopropenylphenol (0.95—1.0 g, 95—100%), m.p. 77—78 °C.

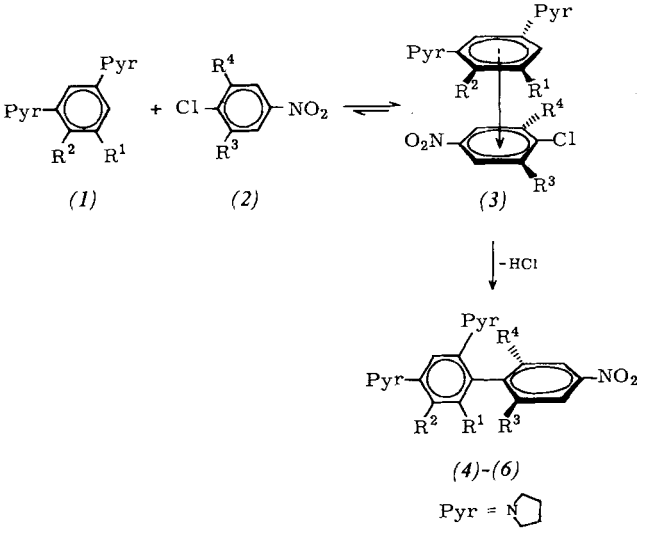
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Nucleophilic Aromatic Substitution: A New Synthetic Route to Biphenyls[1]

By *Franz Effenberger, Klaus Nagel*, and *Wolfgang Agster*[*]

The most important methods for preparation of biphenyls are the Ullmann[2] and Gomberg reactions[3], which involve radical or organometallic intermediates; furthermore, biaryls are formed by benzidine rearrangement[4] and oxidative dimerization[5], as well as in the course of reactions involving aryne intermediates[6].



	R^1	R^2	R^3	R^4
(4a)	Pyr	CH_3	NO_2	NO_2
(5a)	Pyr	H	NO_2	NO_2
(5b)	Pyr	H	CN	NO_2
(5c)	Pyr	H	$COOCH_3$	NO_2
(5d)	Pyr	H	COOH	NO_2
(5e)	Pyr	H	H	NO_2
(5f)	Pyr	H	H	CN
(6a)	H	H	NO_2	NO_2
(6b)	H	H	$COOCH_3$	NO_2

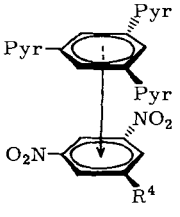
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By treating aminobenzenes *(1)* with reactive haloarenes *(2)*, we have now obtained a polar aryl-aryl linkage *via* nucleophilic aromatic substitution, yielding biphenyl derivatives *(4)* to *(6)*.

In all cases, closure of the new C—C bond is preceded by formation of charge-transfer (CT) complexes *(3)* which may be isolated in crystalline form if reaction conditions are kept sufficiently mild. Only when heated do the CT complexes lose HCl to give biphenyls *(4)* to *(6)* (Table 1). The reactivity of the components *(1)* and *(2)* may be varied within wide limits. When tripyrrolidinobenzene is treated with chlorotrinitrobenzene *(2a)* the reaction mixture begins to boil. Upon introduction of an alkyl group R^2 into the aminobenzene *(1)*, the two *ortho* pyrrolidino rings are twisted out of the aromatic ring plane[7, 8]; reduced mesomeric interaction results in a decrease in electron density and thus also in the reactivity at the free ring positions. Consequently, heating is required for reaction of 1-methyl-2,4,6-tripyrrolidinobenzene with *(2a)*; with 1-ethyl-2,4,6-tripyrrolidinobenzene, the reaction does not proceed beyond the CT complex stage. For the haloarenes, 2-chloro-4-nitrobenzoic acid represents about the limit of reactivity towards tripyrrolidinobenzene.

The structure of the new biaryls is established by elemental analyses, molecular-weight determinations, and NMR spectra. Unexpectedly, compounds *(4)* to *(6)* are obtained as dark red to black, shiny crystals; from position, intensity, and structure of the visible absorption bands which determine the color (Table 1), interpretation as charge-transfer transitions is rather likely. Intermolecular CT interaction can be ruled out since Lambert-Beer's law holds unambiguously even at low concentrations. For a check, we have prepared comparable CT complexes *(7)*, which, as expected, show increasing dissociation as the concentration is lowered.

The geometry of the biphenyls *(4)* to *(6)* is fixed to a large extent, thus allowing a more detailed study of the intramolecular charge transfer on which we report in the accompanying Communication[9].



(7a), $R^4 = NO_2$
(7e), $R^4 = H$

Lowest-energy absorption of *(7a)* (630 nm in CH_2Cl_2)

c	7×10^{-3}	7×10^{-4}	7×10^{-5}
d	0.1 cm	1.0 cm	10.0 cm
E	0.31	0.05	*ca.* 0.01

Table 1. Biphenyls *(4)* to *(6)* obtained from aminobenzenes *(1)* and chlorobenzenes *(2)*.

	Yield (%)	M. p. (°C)	λ_{max} (nm); $\varepsilon_{\lambda,max}$ in CH_2Cl_2	
(4a)	78	189–190	572.5; (3860)	424.5; (4870)
(5a)	79	174–176	587 ; (6300)	414 ; (3560)
(5b)	76	203	560 ; (6140)	416 ; (2180)
(5c)	57	186	549 ; (5700)	sh
(5d)	59	198	*ca.* 535 ; (sh)	426.5
(5e)	85	209–210	524.5; (6690)	395 ; (2650)
(5f)	64	212	484.5; (5680)	405 ; (1440)
(6a)	77	179	563 ; (6820)	427 ; (3200)
(6b)	84	148	523 ; (6650)	sh

Methyl 2,4-dinitro-2',4'-dipyrrolidino-6-biphenylcarboxylate (6b):

Methyl 2-chloro-3,5-dinitrobenzoate *(2c)* (3.66 g, 0.016 mol) in solution in ethanol (15 ml) is added to 1,3-dipyrrolidinobenzene (6.48 g, 0.03 mol) in $CHCl_3$ (15 ml). The mixture, which at once turns dark red, is briefly boiled and then treated with ethanol (50 ml). On cooling, almost black crystals of the CT complex *(3)* deposit ($R^1=R^2=H$, $R^3=COOCH_3$, $R^4=NO_2$) (84%), m. p. 79 °C, $\lambda_{max}=537$ nm ($E=0.27$; 3.3×10^{-3} M in CH_2Cl_2). Complex *(3)* is redissolved in the mother-liquor by warming and heated under reflux for 4 h. After cooling, the biphenyl *(6b)* is precipitated in dark red crystals; it can be recrystallized from ethanol-light petroleum.

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Intramolecular Charge Transfer in (Dialkylamino)nitrobiphenyls[1]

By *Ewald Daltrozzo*, *Franz Effenberger*, and *Peter Fischer*[*]

The deep color of the new biaryls reported in the previous Communication[2] must be ascribed to a charge transfer (CT) transition. Since within the region $7.5\cdot10^{-4}$ to $7.5\cdot10^{-6}$ mole/liter the absorption is independent of concentration, intermolecular origin of this CT interaction can be ruled out. For interpretation of intramolecular charge-transfer processes, knowledge of the molecular geometry is a prerequisite: information about the structure of the biphenyls *(1)* to *(3)* may be gained from the ^{1}H-NMR spectra.

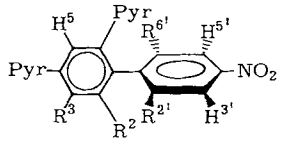
In *(1a)* and *(2a)* to *(2f)*, the signals of the *ortho*-pyrrolidino groups are shifted to higher field by about 0.30 ppm (β-methylene protons) and 0.60 ppm (N—CH_2) respectively, relative to those of the para-amino substituents (Table 1). Improved shielding due to steric hindrance of resonance by the nitrophenyl substituents[2] does not suffice to account for these large shifts, especially of the β-CH_2 hydrogen nuclei[3]; it must rather be assumed that the *ortho*-dialkyl-

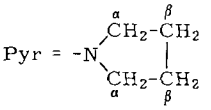
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amino groups protrude deep into the diamagnetic anisotropy field of the nitrobenzene. The characteristic structure of the methylene multiplets, though, is not split further; within the NMR-time scale, the NR_2 groups must therefore be placed symmetrically with respect to the plane of the nitroarene [cf. *(4)*].

Admixture of contact charge transfer in chlorinated hydrocarbons gives a bathochromic shift. As has been observed for tetracyanoethylene[6], CH_2Cl_2 is a far more effective donor than CCl_4; for interaction of the amino system with halomethanes as acceptors[7], the opposite effect is to be expected.

Table 1. ^{1}H-NMR data and longest-wave UV absorptions of biphenyls *(1)* to *(3)*.

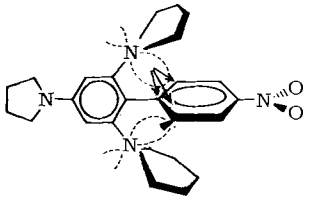




	R^2	R^3	$R^{2'}$	$R^{6'}$	NMR (τ values); 0.5 M in $DCCl_3$, int. TMS, 30 °C Pyr, β-H [a]	Pyr, α-H [a]	$H^{3,5}$	$H^{3',5'}$	λ_{max} (nm); (ε_{max}) [b]
(1a)	Pyr	CH_3	NO_2	NO_2	8.28 (o) 8.05 (p)	7.22 (o) 6.73 (p)	3.57	1.19	548.5; (3520)
(2a)	Pyr	H	NO_2	NO_2	8.30 (o) 7.99 (p)	7.26 (o) 6.65 (p)	4.01	1.26	561.5; (5750)
(2b)	Pyr	H	CN	NO_2	8.29 (o) 7.99 (p)	7.23 (o) 6.63 (p)	3.97	$H^{3'}$ 1.36 $H^{5'}$ 1.19	532.5; (5940)
(2c)	Pyr	H	$COOCH_3$	NO_2	8.32 (o) 7.99 (p)	7.28 (o) 6.65 (p)	4.01	1.31 1.28	530.5; (5660)
(2d)	Pyr	H	COOH	NO_2	8.22 (o) 7.96 (p)	7.14 (o) 6.65 (p)	3.97	1.41 1.22	466 ; (3480)
(2e)	Pyr	H	H	NO_2	8.31 (o) 7.99 (p)	7.26 (o) 6.65 (p)	4.01	$H^{3'}$ 1.32 $H^{5'}$ 1.71 $H^{2'}$ 2.31	510.5; (5790)
(2f)	Pyr	H	H	CN	8.31 (o) 7.99 (p)	7.24 (o) 6.64 (p)	3.99	$H^{3'}$ 1.52 $H^{5'}$ 1.70 $H^{2'}$ 2.32	472 ; (6230)
(3a)	H	H	NO_2	NO_2	8.23 (o) 7.98 (p)	7.09 (o) 6.65 (p)	H^2 3.14 H^3 3.61 H^5 3.93	1.32	533 ; (5960)

[a] (o) denotes pyrrolidino substituents in the 2- and 6-positions, (p) those in the *p*-position to the biphenyl linkage; in each case, the center of the characteristic multiplet is given as the signal position.
[b] 7.5×10^{-5} M in CH_3CN.

In *(2d)*, a hydrogen bridge can be formed from the COOH group to the *ortho*-dialkylamino-nitrogen; the resulting decrease in electron density on the N-atom shifts the $N-CH_2$ signal by -0.14 ppm. This shows how sensitive the NMR signals are even to small changes in structure.



(4)

Therefore the fact that the $H^{3',5'}$ signal position is almost identical for *(2a)* to *(2f)* (while electron affinities of the nitrophenyl units differ widely) seems to us good proof that in the ground state there is no significant interaction between the two aromatic component systems.

While several papers on intramolecular CT complexes have recently been published[4], intramolecular CT interaction in biphenyls has not been observed previously. The near constancy of the band position for *(2a)* over a series of solvents (Table 2) again ascertains the intramolecular origin of the longest-wave absorption of *(1)* to *(3)*.

Gradation of band positions in the order *(2a)*→*(1a)*→*(3a)* (561.5, 548.5, 533 nm), as well as for the sequence *(2a)*→*(2f)*, shows the energy of the CT transition to be determined by both the electron density of the amino and the electron affinity of the acceptor component. There is no straightforward correlation, though, with the $E_{1/2}^{Red}$ values of the nitroarenes.

For an interpretation of the charge transfer several possible mechanisms must be taken into account:

(a) interaction of the n-electron pair of one *ortho*-nitro-oxygen atom and orbitals of C-2 and C-6 of the aromatic amine;

(b) direct interaction between the lone pair of the *ortho*-pyrrolidino nitrogen and, particularly, positions 1', 2', and 6' of the aromatic nitro compound [see *(4)*];

(c) "normal" charge transfer from the electron-rich amino to the electron-deficient nitro component (overlap between p_z orbitals of one aromatic system and σ orbitals of bonds 1—2 and 1—6 of the other arene).

Transfer between the amino benzene and the *ortho*-nitro groups as in (a) is rather unlikely since, on the basis of orbital symmetry, there is no bonding interaction between any of the molecular orbitals participating in the long-wave transitions. By PPP calculations[8], position and intensity of the lowest-energy absorption may be reprod-

uced satisfactorily even without taking process (b) into account, and without specific adjustment of parameters[9,10]! Thus, in the first electron transition (CT band), charge is transferred primarily from the *ortho* nitrogen atoms and from C-1 of the aminobenzene to C-1′ and the *ortho*-nitro groups of the second component; hyperconjugative σ-π interaction as in (c) has been taken into account by introducing pseudo-π centers.

Table 2. Lowest-energy UV-absorption bands of *(2a)* in various solvents.

	C_6H_{12}	CCl_4	Dioxane	Dimethoxyethane	CH_2Cl_2	Acetone	CH_3CN	CH_3OH
E_T-value [5]	31.2	32.5	36.0	38.2	41.1	42.2	46.0	55.5
$\tilde{\nu}$ (cm^{-1})	17940	17610	17970	17950	17040	17860	17810	18050
$\Delta\tilde{\nu}_{1/2}$ (cm^{-1})	3730	3930	4620	5010	4620	5090	5090	5250
ε_{max}	7240	7030	5720	5740	6300	5690	5750	5560

An estimate as to the relative contributions of mechanisms (b) and (c) to the charge transfer observed will be possible as soon as dialkylamino biphenyls become available with different gradation between N-basicity and π-electron density at the free aromatic ring positions.

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German version: Angew. Chem. *83*, 621 (1971)

[1] We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

[2] *F. Effenberger, K. Nagel,* and *W. Agster,* Angew. Chem. *83*, 619 (1971); Angew. Chem. internat. Edit. *10*, 566 (1971).

[3] The appreciably more bulky isopropyl group causes a shift to higher field of only 0.25 (α-H) or 0.07 ppm (β-H); because of the strongly anisotropic NO_2 groups an additional paramagnetic shift is also to be expected.

[4] *K. Mutai,* Tetrahedron Lett. *1971*, 1125; *H. A. H. Craenen, J. W. Verhoeven,* and *Th. J. de Boer, ibid. 1970*, 1167; for a review of previous literature see *R. Foster,* Organic Charge Transfer Complexes, Academic Press, London 1969, p. 78.

[5] *Ch. Reichardt* and *K. Dimroth,* Fortschr. Chem. Forsch. *11*, 1 (1969).

[6] *R. X. Ewall* and *A. J. Sonnessa,* J. Amer. Chem. Soc. *92*, 2845 (1970).

[7] *K. M. C. Davis* and *M. F. Farmer,* J. Chem. Soc. *B 1968*, 859.

[8] *R. Pariser* and *R. G. Parr,* J. Chem. Phys. *21*, 466, 767 (1953); *J. A. Pople,* Trans. Faraday Soc. *49*, 1375 (1953).

[9] Parametrization: *F. Dörr, G. Hohlneicher,* and *S. Schneider,* Ber. Bunsenges. Phys. Chem. *70*, 806 (1966).

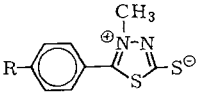
[10] We thank Drs. *G. Hohlneicher* and *S. Schneider* for supplying the computer program. The calculations were carried out on the TR4 installation at the Leibniz-Rechenzentrum of the Bayerische Akademie der Wissenschaften.

X-Ray Photoelectron Spectroscopy of Mesoionic Compounds

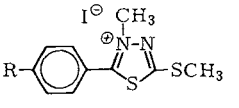
By *Manfred Patsch* and *Peter Thieme*[*]

Photoelectron spectroscopy (ESCA)[1] makes it possible to determine the binding energy of core electrons, this energy appearing as the difference between the excitation energy and the kinetic energy of the emitted electrons. Since the excitation energy is an imprecise quantity the method becomes rather inaccurate and requires that there shall be considerable charge differences in the atoms that are to be differentiated. Such large charge differences are found among mesoionic heterocycles, being recognizable in the large dipole moments of these compounds. Dipole moments have previously formed the basis for study of the structure of, and charge distribution in, mesoionic compounds[2]. As the following results show, the ESCA method can be used to obtain further information.

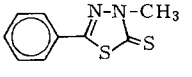
We have determined the X-ray photoelectron spectra (ESCA spectra)[3] of 3-methyl-2-phenyl-1,3,4-thiadiazole-5-thiones *(1)*[4] and *(2)*[5] (recorded as mesoionic compounds in the literature), their methiodides *(3)* and *(4)*[6], as well as phenylsydnone *(6)*[7].



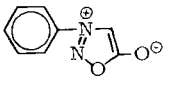
(1), R = H
(2), R = Cl



(3), R = H
(4), R = Cl



(5)



(6)

The binding energies of the nitrogen-1*s* electrons in *(1)* and *(2)* differ by about 2.3 eV (Fig. 1), in the methiodides *(3)* and *(4)* by about 1.2 eV (Fig. 2). For the sulfur-2*p* electrons in *(1)* and *(2)* a difference in binding energy of about 2.5 eV is found (Fig. 1). In *(3)* and *(4)* the 2*p* electrons of the two sulfur atoms show a single signal (Fig. 2), *i.e.* here the sulfur atoms are equivalent in respect of their charge densities; their electron-binding energy corresponds to that of thioethers.

In 4-methyl-2-phenyl-1,3,4-thiadiazole-5-thione *(5)*[8], which is isomeric with *(1)*, the difference in binding energy of the N-1*s* electrons is only 0.9 eV, and that of the S-2*p* electrons 2.1 eV. The charge separation in *(5)* is thus distinctly smaller than in *(1)*, as is also expressed in the dipole moments (Table 1). Two values were also found for the nitrogen- and oxygen-1*s* electrons in phenylsydnone *(6)* (Table 1).

The electron-binding energies obtained by the ESCA method depend on the shielding of nuclear charge by the electronic environment and are larger the smaller the shielding or the larger the effective nuclear charge; according to *Siegbahn et al.*[11] this dependence is approximately linear. The ESCA values are also related to the electronegativity of the atoms concerned and of attached atoms;

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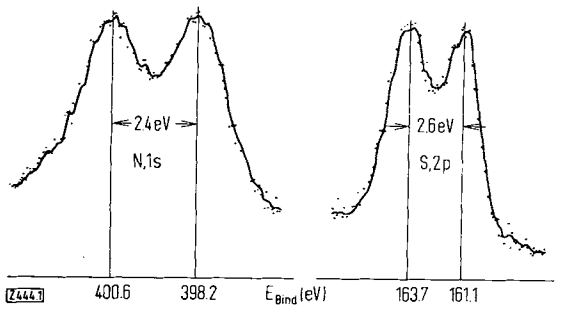


Fig. 1. X-ray photoelectron spectra of *(1)*.

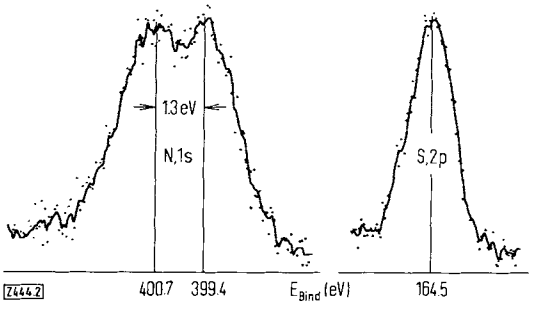


Fig. 2. X-ray photoelectron spectra of *(3)*.

they can be correlated satisfactorily with the units of charge obtained from the Pauling electronegativity relations[10]. Thus a difference of 2.3 eV for the binding energy of the N-1*s* electrons in *(1)* and *(2)* corresponds to a charge difference of 0.46 charge unit. *Carlson* found a comparable value for 7-methylinosine, a typical betaine, with 2.6 eV ≡ 0.52 charge unit[11]. The difference of 2.5 eV for the S-2*p* electrons in *(1)* and *(2)* represents, by a similar calculation, a charge difference of 0.49 charge unit. These results confirm *Katritzky*'s view that a betaine structure predominates in the ground state of mesoionic 1,3,4-thiadiazolethiones and similar compounds, with charge distribution as shown in the formulations *(1)*, *(2)*, and *(6)*.

Table 1. X-ray photoelectron spectra and dipole moments of compounds *(1)* to *(6)* [a].

	N,1*s*(eV)	ΔE_B(eV)	S,2*p*(eV)		ΔE_B(eV)	Dipole moment μ(D)
(1)	398.2; 400.6	2.4	161.1;	163.7	2.6	9.28 ± 0.1
(2)	398.3; 400.5	2.2	160.7;	163.2	2.5	8.13 ± 0.02
(3)	399.4; 400.7	1.3		164.5	0	
(4)	399.1; 400.1	1.0		163.5	0	
(5)	399.7; 400.6	0.9	161.6;	163.7	2.1	4.32 ± 0.06 [9]
(6)	399.4; 401.4	2.0	O,1*s*: 530.3;	532.7	2.4	6.48 ± 0.02 [9]

[a] The spectra of compounds *(3)* to *(6)* were resolved by a DuPont curve analyzer model 310.

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[1] a) *K. Siegbahn et al.*: ESCA, Atomic, Molecular and Solid State Structure Studies by Means of Electron Spectroscopy. Almquist & Wiksells, Uppsala 1967; b) *J. M. Hollander* and *W. L. Jolly*, Accounts Chem. Res. *3*, 193 (1970); c) *D. M. Hercules*, Anal. Chem. *42*, 20A (1970).

[2] *A. R. McCarthy* and *W. D. Ollis et al.*, J. Chem. Soc. *B 1969*, 1185.

[3] The spectra were measured on a Varian IEE-15 instrument. The Al-$K\alpha_{1,2}$ line (1486 eV) provided the activation energy. The instrument was adjusted so that the Au-$4f_{7/2}$ line fell at 83.0 eV. The electron-binding energies given were standardized on the C-1*s* signal from Tesa film (= 284 eV).

[4] *R. Grashey, M. Baumann*, and *W.-D. Lubos*, Tetrahedron Lett. *1968*, 5881.

[5] *K. T. Potts* and *C. Sapino*, Chem. Commun. *1968*, 672.

[6] The methiodides are conveniently obtained from the mesoionic compounds by means of methyl iodide in boiling acetonitrile.

[7] *C. J. Thoman* and *D. J. Voaden*, Org. Synth. *45*, 96 (1965).

[8] *F. C. Hengebaert* and *J. F. Willems*, Tetrahedron *22*, 913 (1966).

[9] *R. W. Hill* and *L. E. Sutton*, J. Chem. Phys. *46*, 244 (1949).

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Nomenclature for Intramolecular Exchange Processes

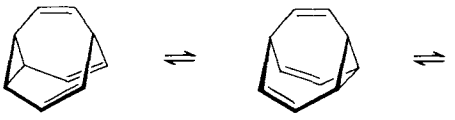
By *Gerhard Binsch, Ernest L. Eliel*, and *Horst Kessler*[*]

We wish to propose a system of nomenclature for describing the interchange of identical ligands between distinguishable chemical and/or magnetic environments. Such interchanges correspond to "null reactions", involving no change in chemical structure, but they can frequently be studied quantitatively by dynamic NMR spectroscopy. Names have been suggested for the process of exchange, notably "degenerate isomerization", "isodynamic change"[1], and "automerization"[2]. We should like to point out that a useful, alternative classification can be based on the recently developed nomenclature[3-5] in which identical ligands in stereochemically different environments are designated as "enantiotopic" or "diastereotopic"[3], the overall term for the two cases being "heterotopic"[4] or "stereoheterotopic"[5]; in contrast, ligands in identical chemical surroundings are called "homotopic"[4-6]. We therefore propose that the process leading to exchange of the positions of identical ligands be called "topomerization"; in this context, it is sometimes convenient to have a name for the indistinguishable species involved in the exchange and we suggest they be called "topomers".

It may sometimes be desirable (and often, though not always, possible) to employ sub-classifications, similar to those used for isomerization. Thus bullvalene *(1)*[9] represents a case of multiple valence bond or constitutional topomerization, whereby one and the same ligand (carbon, hydrogen) is placed in four chemically different positions

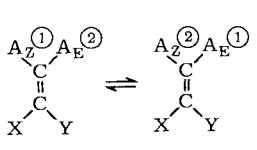
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(allylic, two kinds of vinylic, cyclopropanoid). Examples of *cis-trans* topomerization or diastereotopomerization of the type *(2)* (*e.g.*: X=CN, Y=C_6H_5, A=$N(CH_3)_2$) have

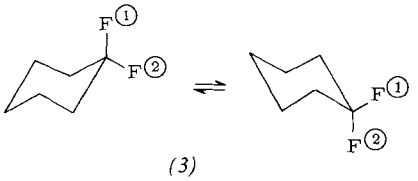


(1)

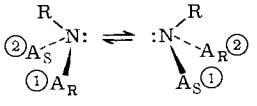
recently been studied[10] by dynamic NMR spectroscopy. Another well-known case of diastereotopomerization is that of the cyclohexane ring inversion, *e.g. (3)*[11]. Enantiotopomerization is represented by *(4)*; the enantiotopic groups A_R and A_S might, in principle, be distinguishable in a chiral solvent when inversion is slow. The



(2)

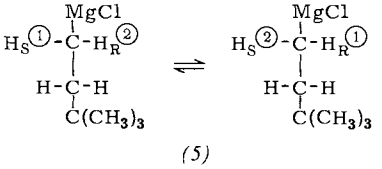


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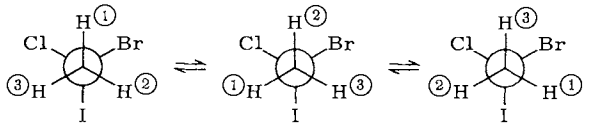


(4)

enantiotopomerization *(5)* has in fact been studied experimentally[12] in achiral solvents. This becomes possible because the enantiotopic nuclei are anisogamous[13]; the methylene proton NMR spectrum of *(5)* changes from an AA'BB' type (or $[AB]_2$ type in the notation of *Haigh*[15]) to an A_2B_2 type on increase of the exchange rate. Case *(6)*, like case *(3)*, may be described as one of conformational topomerism[16, 17].

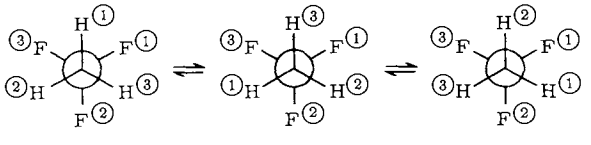


(5)



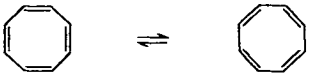
(6)

In the examples *(1)*—*(6)* the exchanging ligands differ in "topicity" and hence we are dealing with "heterotopomerizations", more specifically, in cases *(2)*—*(6)*, with "stereoheterotopomerizations". But even if the exchanging ligands are homotopic, the exchange process may still be



(7)

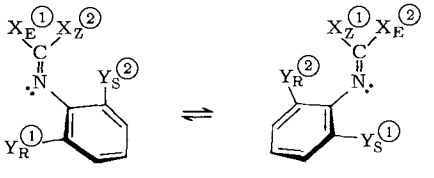
detectable by dynamic NMR spectroscopy. The internal rotation in 1,1,1-trifluoroethane *(7)* provides an example of such a "homotopomerization". Here the three hydrogen atoms (and also the three fluorine atoms) are structurally equivalent in each of the three conformers, but the expected inequality of the *gauche* and *anti* hydrogen-fluorine coupling constants should lead to spectra of the $[AX]_3$ type[15] when rotation is slow on the NMR time scale and of the $[A_3X_3]$ type in the fast-exchange limit. The bond-shift process in cyclooctatetraene *(8)* represents another intriguing case of (constitutional) homotopomerization,



(8)

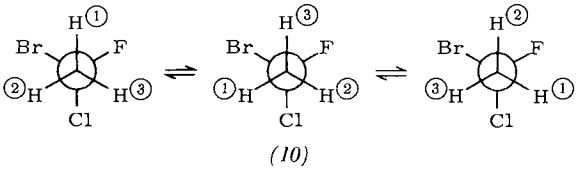
detectable in principle from a study of [per-^{13}C]cyclooctatetraene, where the spectrum pertaining to the averaged planar form would be of the $[[AX]_2]_4$ or $[AX]_8$ type depending on the rate of the bond-shift process[18].

Finally we wish to point out that a detailed classification of topomerization processes and/or of topomers along the lines suggested in this note may not always be possible.

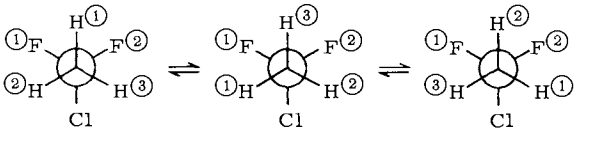


(9)

The in-plane nitrogen inversion process *(9)*[20], which simultaneously interchanges the diastereotopic ligands X and the enantiotopic ligands Y, can be characterized uniquely (as enantiotopomerization or diastereotopomerization) with reference to specific ligands, but the classification of the topomers involved would necessarily have to be ambiguous. Similarly, the internal rotation *(10)* corresponds to a homotopomerization with respect to the fluorine ligand, but to a diastereotopomerization with respect to the three hydrogen atoms. Finally case *(11)*, a homotopomerization with respect to either fluorine atom, is a "mixed" topomerization with regard to the three hydro-



(10)



(11)

gen atoms. ("Mixed" because positions labeled 2 and 3 in the first conformer on the left are enantiotopic and 2 and 1—or 3 and 1—are diastereotopic.) Both cases *(10)* and *(11)* represent heterotopomerization with respect to the hydrogen atoms. The even more complicated situation in

the stereochemically nonrigid six-coordinate molecule $FeH_2[P(OC_2H_5)_3]_4$ has recently been analyzed quantitatively[21].

We believe that a detailed nomenclature capable of coping with the most general case would become so unwieldy as to lose its appeal for the majority of situations commonly encountered in practice. For a rigorous description of very complex topomerizations it will clearly be necessary to resort to a formal permutational approach.

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[2] *A. T. Balaban* and *D. Farcasiu*, J. Amer. Chem. Soc. *89*, 1958 (1967).

[3] *K. Mislow* and *M. Raban*, Top. Stereochem. *1*, 1 (1967).

[4] *D. Arigoni* and *E. L. Eliel*, Top. Stereochem. *4*, 127 (1969).

[5] *K. R. Hanson* and *H. Hirschmann*, personal communication; see also *E. L. Eliel*, J. Chem. Educ. *48*, 163 (1971).

[6] For prochiral enantiotopic and diastereotopic ligands [3] we use the designations L_R and L_S defined elsewhere [4, 7]; heterotopic ligands in an olefin are denoted by L_Z and L_E [8].

[7] *K. R. Hanson*, J. Amer. Chem. Soc. *88*, 2731 (1966).

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[10] a) *H. Kessler*, Angew. Chem. *82*, 237 (1970); Angew. Chem. internat. Edit. *9*, 219 (1970); b) *H. Kessler*, Chem. Ber. *103*, 973 (1970).

[11] *S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan*, and *J. D. Roberts*, J. Amer. Chem. Soc. *89*, 88 (1967).

[12] *G. M. Whitesides, M. Witanowski*, and *J. D. Roberts*, J. Amer. Chem. Soc. *87*, 2854 (1965).

[13] This term, suggested by *Laszlo* [14], is self-explanatory and descriptive, whereas the ambiguous "magnetically nonequivalent" and even the more specific "spin-coupling nonequivalent" [3] are misleading unless explicitly curtailed by restrictive definitions [3].

[14] *P. Laszlo*, personal communication.

[15] *C. W. Haigh*, J. Chem. Soc. *A 1970*, 1682.

[16] For cases of this type, see *W. E. Heyd* and *C. A. Cupas*, J. Amer. Chem. Soc. *91*, 1559 (1969) and reference [10a].

[17] Topomerization by rotation about the carbon-carbon bond of *(6)* is confined to cyclic permutations (123⇌231⇌312); the remaining permutational possibilities (213, 132, 321) are inaccessible by rotation. The situation could be characterized by an extension of the Cahn-Ingold-Prelog rules, where the labeling determines the priority sequence and the "configurational" symbol is enclosed in square brackets. In the topomers of *(6)* the methyl group then belongs to the [*R*] family.

[18] This experiment has not been carried out, but we known about the bond-shift process from an NMR study of the closely related heterotopomerization in [mono-^{13}C]cyclooctatetraene [19].

[19] *F. A. L. Anet*, J. Amer. Chem. Soc. *84*, 671 (1962).

[20] *H. Kessler* and *D. Leibfritz*, Chem. Ber. *104*, 2143 (1971).

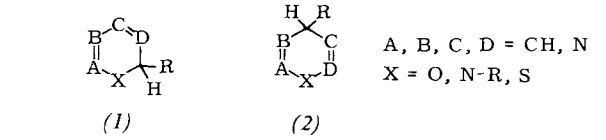
[21] *P. Meakin, L. J. Guggenberger, J. P. Jesson, D. H. Gerlach, F. N. Tebbe, W. G. Peet*, and *E. L. Muetterties*, paper presented at the Symposium on Dynamic NMR Spectroscopy, Los Angeles, Calif., March 30, 1971.

Synthesis of a 6-Oxa-2-azabicyclo[3.1.0]hex-3-ene: Heterocyclic 8π-Systems as Reactive Intermediates[**]

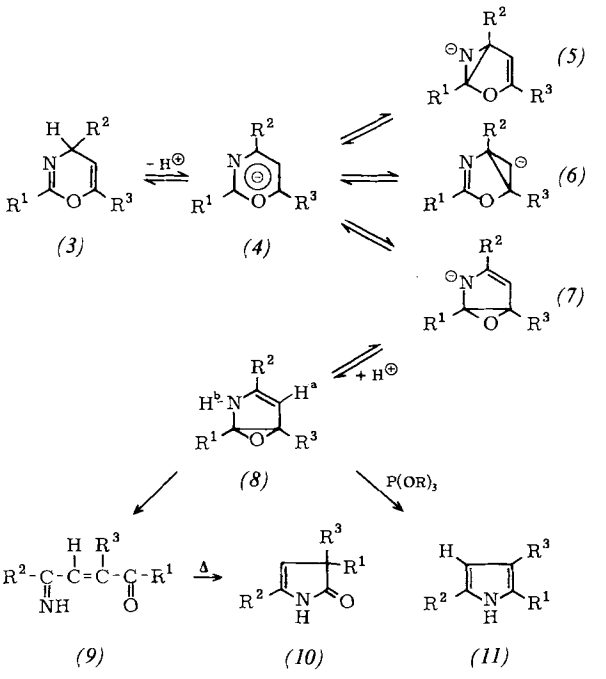
By *Richard R. Schmidt*[*]

Cyclic conjugated planar $4n$-π systems are destabilized by resonance and according to *R. Breslow*[1] are antiaromatic. The electronic destabilization confers high reactivity on these systems, which thus become interesting intermediates.

Planar systems, as small as possible, with bond angles of *ca.* 120°[2] are particularly advantageous models for antiaromatic behavior. Such systems should be readily obtainable in the heterocyclic series if one starts from six-membered dihydro heterocycles *(1)* and *(2)*[3]. If these are converted into the corresponding anions, substantially planar 8π electron systems result.



(1) *(2)*



(3) *(4)* *(5)* *(6)* *(7)* *(8)* *(9)* *(10)* *(11)*

4*H*-1,3-Oxazine *(3)* was used as an example. When it is treated with butyllithium in anhydrous tetrahydrofuran (THF) at −78 °C a deep blue intermediate (λ_{max}^{THF} = 570; 612 nm)[4] is formed, to which we ascribe the structure *(4)*. This 8π system undergoes rapid further reaction, yielding a new, colorless product. For an intramolecular reaction the conversion into especially the valence-tautomeric anions *(5)*, *(6)*, and *(7)* must be taken into account. The anion *(7)* is thermodynamically more stable than *(5)* or *(6)*, and indeed careful working up of the reaction mixture permits isolation of a compound whose analytical and spectroscopic data and subsequent reactions accord only with its formulation as the triphenyl derivative *(8)* of the previously unknown 6-oxa-2-azabicyclo[3.1.0]hex-3-ene[5].

In protic solvents compound *(8)* rearranges rapidly, even at room temperature, into the open-chain iminobutenone *(9)* (in ethanol, $\tau_{1/2}^{20\,°C}$ = 2 h), presumably in a pericyclic $[\sigma_s^2+\sigma_s^2+\pi_s^2]$ reaction. On thermolysis, the pyrrolinone *(10)*[6] is obtained from *(8)* by way of *(9)*. By variation of the substituents R^1, R^2, and R^3 it can be proved that in this reaction R^1 migrates to the C atom to which R^3 is bonded[7]. On treatment of *(8)* with triethyl phosphite the pyrrole *(11)* is formed in 50% yield.

The equilibrium between *(4)* and *(7)* lies much to the side of the latter; it can also be set up from *(8)*[7]. The

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chemical and physical properties of the intermediate *(4)* are under further investigation.

Experimental:

1,3,5-Triphenyl-6-oxa-2-azabicyclo[3.1.0]hex-3-ene (8)

Compound *(3)* (1.87 g, 6 mmol) is dissolved in anhydrous THF (40 ml). *n*-Butyllithium as 20% solution in hexane (4 ml) is added dropwise to the above reaction mixture under nitrogen at −78 °C (bath temperature) within 5 min. After 20 min the mixture is worked up at 0 °C with water and chloroform, and the organic phase is dried with K_2CO_3. The solid product remaining on evaporation is treated with a little cold ethanol, filtered off rapidly, well dried, and recrystallized in small portions from anhydrous cyclohexane. M.p. 130—145 °C with rearrangement to *(10)*. Yield 1.27 g (68%) of *(8)*.

Spectra of (8):

UV: $\lambda_{max}^{CCl_4}$ = 345, 267 nm, lg ε = 3.47, 4.47.

IR: between 1550 and 1700 cm^{-1} there is only a weak band at 1594 cm^{-1}, which is assigned to the phenyl nuclei.

NMR (in $CHCl_3$ with TMS as internal standard): H^a = 3.76, H^b = 6.45. In $CDCl_3$/L-α-phenylethylamine (4:1) splitting of H^a into two signals shows that *(8)* exists as a pair of enantiomers.

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[1] *R. Breslow*, Angew. Chem. *80*, 573 (1968); Angew. Chem. internat. Edit. *7*, 565 (1968).

[2] *M. J. S. Dewar* and *G. J. Gleicher*, J. Amer. Chem. Soc. *87*, 685 (1965).

[3] A formally uncharged 8π electron system is obtained if the CHR is replaced by an atom or group of atoms having a free electron pair.

[4] We thank Dr. *G. Hoffmann*, Institut für physikalische Chemie, Universität Stuttgart, for measuring the low-temperature UV spectrum.

[5] There is no proof of structure for the 6-oxa-2-azabicyclo[3.1.0]hex-3-ene derivative mentioned by *L. Chierici* and *A. Cella*, Ann. Chim. (Rome), *43*, 141 (1953); Chem. Abstr. *48*, 8777a (1954).

[6] *F. R. Japp* and *F. Klingemann*, J. Chem. Soc. *57*, 692 (1890).

[7] *R. R. Schmidt, A. Hoffmann*, and *W. Mayer*, unpublished work.

Dichloromethylenedimethylammonium Chloride ("Phosgene Immonium Chloride")[**]: A Versatile Immonium Salt[1]

By *Heinz Günter Viehe* and *Zdenek Janousek*[*]

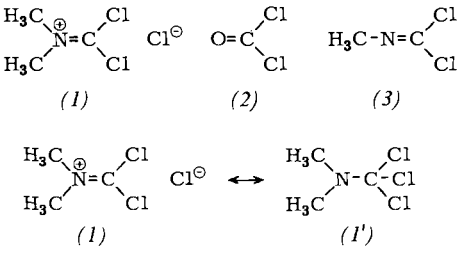
Dedicated to Professor F. Bohlmann on the occasion of his 50th birthday

Owing to its greater double bond polarization the immonium salt dichloromethylenedimethylammonium chloride *(1)* should be more reactive than phosgene *(2)* and methylchloroformimidoyl chloride *(3)* in nucleophilic chlorine substitution.

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[**] Trade name (Aldrich).

The dissociation equilibrium between the salt *(1)* and the covalent structure *(1')* is almost completely displaced in favor of the salt.



(1) *(2)* *(3)*

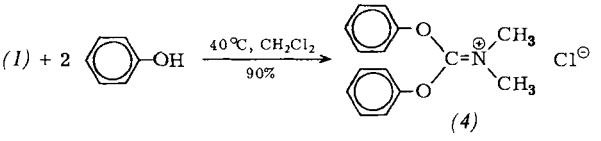
(1) *(1')*

In spite of this expected reactivity[2] and of the many potential synthetic applications of the related compounds *(2)* and *(3)*[3], compound *(1)* has hardly been studied so far. Thus *(1)* is mentioned as a white salt which explodes on heating[4] and which produces dimethylcarbamoyl chloride on hydrolysis[4, 5]. Diethyl and bis(*p*-Cl—C_6H_4) analogs have been described as intermediates in the synthesis of trifluoromethylamines[5, 6].

It is the purpose of this communication to report on the chemical and spectroscopic characterization of *(1)*. Compound *(1)* is obtained in about 90% yield by chlorination of tetramethylthiuram disulfide in CH_2Cl_2 and is isolated as a white hygroscopic solid[4], m.p. about 180 °C (decomp.); IR (Nujol): 1625 cm^{-1}; NMR (CD_3NO_2): δ = 4.07 ppm (s)[7].

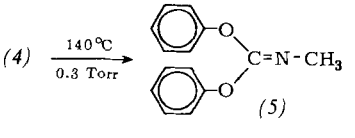
Pyrolysis of *(1)* begins at about 130 °C and becomes very rapid at 190 °C. The principal product is *(3)*, which proved to be identical with an authentic sample[8].

Refluxing *(1)* (2.65 g, 16.4 mmol) with phenol (3.10 g, 32.8 mmol) in CH_2Cl_2 (15 ml) for one hour produces the ammonium salt *(4)* (4.1 g, 90%); NMR ($CDCl_3$): δ = 3.76 (6H,s) and 7.25 ppm (10H,m); IR ($CHCl_3$): 1710, 1600, and strong absorption between 1150 and 1250 cm^{-1}. Hydrolysis of *(4)* by acid or base yields diphenyl carbonate.



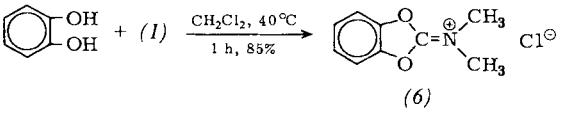
(4)

Pyrolysis of *(4)* (4.1 g at 140 °C/0.3 torr) generates the new compound diphenyl *N*-methyliminocarbonate *(5)*. The resulting oil was distilled at 100 °C/0.3 torr (3.0 g,



(5)

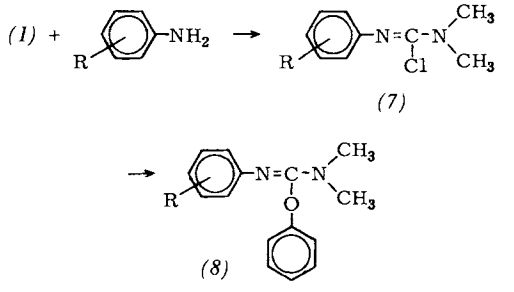
91%); m.p. 42 °C (from pet. ether); NMR ($CDCl_3$): δ = 3.03 (3H,s), 7.20 ppm (10H,m); IR ($CHCl_3$): 1710, 1590, 1490, and a large peak at about 1200 cm^{-1}; mass spectrum: 227 (M^+), 134, 106, 94.



(6)

Pyrocatechol reacts with *(1)* in the same manner as phenol, forming the analogous immonium salt *(6)*, which is characterized by its facile hydrolysis to *o*-phenylene carbonate.

Ammonolysis of *(1)* with liquid ammonia gives dimethylcyanamide in 35% yield. Reaction of *(1)* with two moles of dimethylamine yields tetramethylurea dichloride, which forms tetramethylthiourea on treatment of the reaction mixture with an aqueous solution of sodium sulfide. Even very weak primary amines produce the corresponding chloroformamidines *(7)* with *(1)*.



(7)

(8)

Cpd.	R	Solvent, temp. (°C)	Yield	NMR ($CDCl_3$), δ (TMS = 0)
(7a)	*p*-$COOC_2H_5$	CH_2Cl_2 40	96	1.23 (3H/s), 3.08 (6H/s), 4.30 (2H/m), 6.82 (2H/d), 7.92 (2H/d)
(7b)	*p*-NO_2	ClC_6H_5 100—110	80	3.22 (6H/s), 6.93 and 8.16 (4H/2 doublets, J = 9 Hz)
(7c)	2,4-$(NO_2)_2$	ClC_6H_5 80	87	2.83 (6H/s), 7—9 (3H)

To synthesize *N,N*-dimethyl-*N'*-*p*-nitrophenyl-*O*-phenylisourea *(8b)*, a solution of sodium phenoxide (3.48 g, 30 mmol) in dioxane (80 ml) is added to a solution of *(7b)* (6.83 g, 30 mmol) in dioxane (200 ml). After 3 hours' stirring at 40 °C the precipitated NaCl is filtered off and the solvent is removed. The oily product is purified by column chromatography on silica gel, yield 3.1 g (35%), m.p. 98—99 °C (from ether); NMR ($CDCl_3$): δ = 3.08 (6H,s), 7.95 (2H,d,J = 8 Hz), the other doublet being covered by the multiplet at δ = 6.73—7.30 ppm (7H); IR ($CHCl_3$): 1640, 1578, 1500, 1330 cm^{-1}; mass spectrum: 286 (M^+), 209, 192, 72.

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[1] Immonium Chemistry, Part 1.

[2] See *Z. Janousek* and *H. G. Viehe*, Angew. Chem. *83*, 615 (1971); Angew. Chem. internat. Edit. *10*, 574 (1971); *H. G. Viehe, Z. Janousek*, and *M.-A. Defrenne*, Angew. Chem. *83*, 616 (1971); Angew. Chem. internat. Edit. *10*, 575 (1971).

[3] *Z. Arnold*, Collect. Czech. Chem. Commun. *24*, 4048 (1959).

[4] *A. Senning*, Chem. Rev. *65*, 388 (1965).

[5] *N. N. Jarovenko* and *A. S. Vasilev*, Zh. Gen. Chem. USSR *29*, 3786 (1959); Chem. Abstr. *54*, 19466 (1960).

[6] *N. N. Jarovenko et al.*, Zh. Gen. Chem. USSR *36*, 1309 (1966); Chem. Abstr. *65*, 16885f (1966).

[7] We thank Mr. *R. Merenyi* (Brussels) for his advice.

[8] *E. Kühle* and *B. Anders*, French Pat. 1405732 (1965); Chem. Abstr. *64*, 9603 (1966).

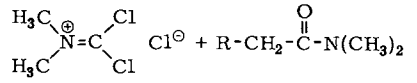
Condensation of Dichloromethylenedimethylammonium Chloride ("Phosgene Immonium Chloride")[**] with *N,N*-Dialkylcarboxamides[1]

By *Zdenek Janousek* and *Heinz Günter Viehe*[*]

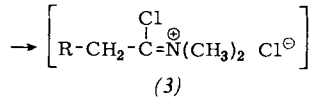
Dedicated to Professor F. Bohlmann on the occasion of his 50th birthday

We have found the immonium salt dichloromethylenedimethylammonium chloride *(1)* to undergo condensation with CH active compounds[2]. Thus when compound *(1)* (0.2 mol) and *N,N*-dimethylcarboxamides *(2)* (0.1 mol) [or their α-chloro immonium chloride derivatives *(3)*] are refluxed together in CH_2Cl_2 or $CHCl_3$ for one to three hours, the new 1,3-dichloromalonylcyanines *(4)* are formed in high yields. During the reaction, heating is continued until the evolution of HCl ceases and a clear solution results. Compounds *(4a)*—*(4d)* crystallize on removal of the solvent; they may be recrystallized from benzene/CH_2Cl_2.

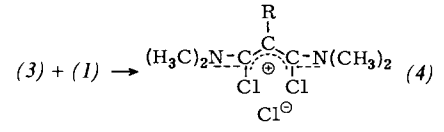
Compounds *(4)* are 1,3-dielectrophiles which permit facile cyclization reactions[2].



(1) *(2)*



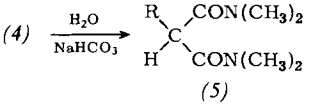
(3)



(4)

Cpd.	R	Yield (%)	M.p. (°C)	NMR ($CDCl_3$), δ (TMS = 0) (ppm)
(4a)	H	91	114–116	3.66 (12H/s), 5.88 (1H/s)
(4b)	C_2H_5	88	65–67	1.2 (3H/t), 2.7 (2H/m), 3.28 and 3.57 (12H, 2 singlets)
(4c)	C_6H_5	90	oil	3.58 (12H/s) 7.4 (5H/m)
(4d)	Cl	88	94	3.68 (12H/s)

Hydrolysis of a suspension of *(4a)*—*(4d)* with aqueous $NaHCO_3$ solution (one hour's stirring) produces the malonylamides *(5a)*—*(5d)*, which can be recrystallized from ether after extraction from the reaction mixture with CH_2Cl_2 and evaporation of the solvent.



(5)

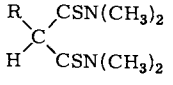
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[**] Trade name (Aldrich).

Cpd.	Yield (%)	M. p. (°C)	IR (CO) (cm^{-1})	Ref.
(5a)	70	[a]	1640 (broad)	[3]
(5b)	75	75–76	1648	—
(5c)	78	149	1642	[4]
(5d)	73	92	1650	—

[a] B. p. 104 °C/0.6 torr.

Treatment of *(4a)*—*(4c)* with H_2S in CH_2Cl_2 in the presence of a threefold excess of triethylamine gives the substituted malonylthioamides *(6a)*—*(6c)*.

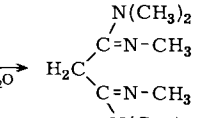


(6)

Cpd.	Yield (%)	M. p. (°C)	NMR ($CDCl_3$), δ (TMS = 0) (ppm)
(6a)	70	106–107	3.42 and 3.53 (12H/2 singlets), 4.37 (2H/s)
(6b)	83	117–118	1.05 (3H/t), 2.23 (2H/m), 3.33 and 3.48 (12H/2 singlets), 3.92 (1 H/t)
(6c)	55	193	3.18 and 3.52 (12H/2 singlets), 5.76 (1H/s), 7.30 (5M/s)

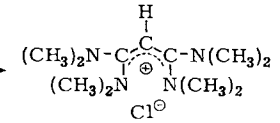
Cpd.	IR ($CHCl_3$) (cm^{-1})	Mass spectrum
(6a)	1510, 1388, 1113, 1097	190 (M^+), 157, 146, 92, 88
(6b)	1500, 1387, 1278	218 (M^+), 189, 146, 130, 98
(6c)	1505, 1387, 1278	266 (M^+), 233, 189, 178, 157

Reaction of *(4a)* with liquid methylamine and subsequently with concentrated KOH solution at −10 °C produces hexamethylmalonylamidine *(7)*; yield 61%, b. p. 75 °C/0.5 torr, NMR ($CDCl_3$): δ = 2.85 (12H,s), 3.08 (6H,s), 3.38 ppm (2H,s); IR (film): 1610, 1370, 1260, 1117, 1050 cm^{-1}; mass spectrum: 184 (M^+), 169, 154, 140.



(7)

In contrast, reaction of *(4a)* with liquid dimethylamine yields tetrakis(dimethylamino)cyanine *(8)*; compound *(8)* can be separated from dimethylammonium chloride as the perchlorate, m. p. 174 °C, which is only sparingly soluble



(8)

in water. The NMR spectrum ($CDCl_3$) shows only one peak for all the N—CH_3 groups at δ = 3.02 ppm and one proton at δ = 3.60 ppm; IR ($CHCl_3$): 1530, 1432, 1400, 1100 cm^{-1}.

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[1] Immonium Chemistry, Part 2.—Part 1: *H. G. Viehe* and *Z. Janousek*, Angew. Chem. *83*, 614 (1971); Angew. Chem. internat. Edit. *10*, 573 (1971).

[2] See [1] and *H. G. Viehe, Z. Janousek*, and *M.-A. Defrenne*, Angew. Chem. *83*, 616 (1971); Angew. Chem. internat. Edit. *10*, 575 (1971); *Z. Janousek*. Thèse de Doctorat, Louvain 1971; *G. de Voghel*, Mém. de Licence, Louvain 1971.

[3] *H. Bredereck*, Chem. Ber. *94*, 2278 (1961).

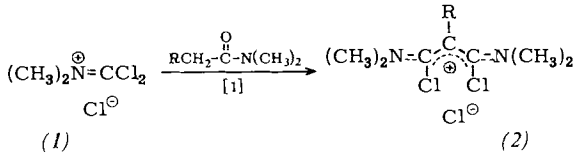
[4] *R. Burgada*, C. R. Acad. Sci. Paris *258*, 1532 (1964).

Reaction of Dichloromethylenedimethylammonium Chloride ("Phosgene Immonium Chloride")[**] with Carbonyl-Activated Methylene Groups[1]

By *Heinz Günter Viehe, Zdenek Janousek*, and *Marie-Agnès Defrenne*[*]

Dedicated to Professor F. Bohlmann on the occasion of his 50th birthday

The immonium salt dichloromethylenedimethylammonium chloride *(1)* reacts readily with protic compounds[2] *via* chlorine substitution. Reaction with *N,N*-dimethylcarboxamides yields the new and versatile dichloromalonylcyanines *(2)*, thus demonstrating the high reactivity of *(1)* towards active methylene groups[1].

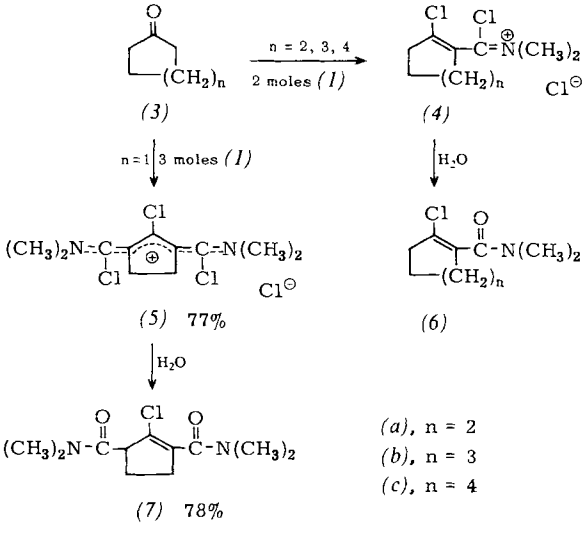


(1) *(2)*

R = H, C_2H_5, C_6H_5, Cl

A similar condensation is now described for *(1)* with carbonyl-activated methylene compounds such as cycloalkanones, phenylacetone, acetophenone, ethyl malonate, and acetoacetates.

Cycloalkanones *(3)* react with *(1)* in refluxing chloroform, either by monocondensation (*n* = 2, 3, 4) or by dicondensation (*n* = 1) to give the immonium chlorides *(4)* or the trichloropentamethinecyanines *(5)*. Hydrolysis of *(4)* and *(5)* gives the amides *(6)* and the diamide *(7)* respectively. The overall yields of *(6a)*, *(6b)*, and *(6c)* amount to 72, 87, and 75% respectively.



(3) *(4)* *(5)* 77% *(6)* *(7)* 78%

(a), n = 2
(b), n = 3
(c), n = 4

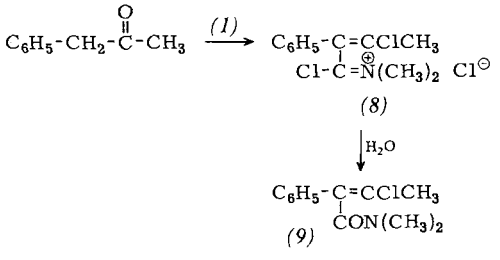
[*] Prof. Dr. H. G. Viehe, Dipl.-Chem. Z. Janousek, and Dipl.-Chem. M.-A. Defrenne
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Naamsestraat 96, B-3000 Louvain (Belgium)

[**] Trade name (Aldrich).

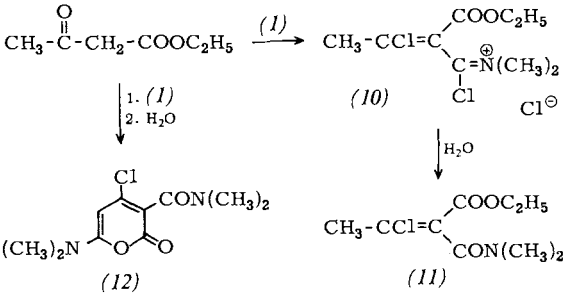
Cpd.	Time (h)	B. p. (°C/torr)	IR ($CHCl_3$) (cm^{-1})
(6a)	3	99–102/0.6	1635, 1497, 1445, 1390, 1130, 1270
(6b)	2	130/0.6	1630, 1492, 1441, 1391, 1264, 1120
(6c)	1	140/0.6	1619, 1480, 1438, 1387, 1262

Cpd.	Mass spectrum	NMR ($CDCl_3$), δ (TMS = 0) (ppm)
(6a)	187 (M^+), 152, 143	1.78 (4H/m), 2.38 (4H/m), 3.00 (6H/s)
(6b)	201 (M^+), 166, 93	1.80 (6H/br.), 2.37 (2H) and 2.65 (2H/br.), 3.00 and 3.05 (6H/2 singlets)
(6c)	215 (M^+), 180	1.62 (8H/br.), 2.30 and 2.55 (4H/2 multiplets), 3.05 and 3.08 (6H/2 singlets)

Phenylacetone reacts with *(1)* to give the expected immonium chloride *(8)* which on alkaline hydrolysis immediately gives the acrylamide *(9)* in 75% overall yield; b. p. 138 °C/0.15 torr; NMR ($CDCl_3$): δ = 2.17 (3H,s), 2.96 (6H,s), 7.26 ppm (5H,s); IR ($CHCl_3$): 1630, 1490, 1440, 1390 cm^{-1}; mass spectrum: 223 (M^+), 188.



Whereas the reactions of *(1)* with simple aliphatic ketones are still under study, the particularly active ethyl acetoacetate was found to give either the expected monocondensation product *(10)*, which is hydrolyzed to the malonic acid derivative *(11)*, or the α-pyrone *(12)* by dicondensation and hydrolysis.



Propio-, benz-, and phenylacetaldehyde reacted only *via* substitution of the oxygen by chlorine and were not examined further.

From the above reactions it would appear that compound *(1)* is generally milder than other Vilsmeier reagents[3].

N,N-Dimethyl-(2-chloro-1-cyclohexenyl)carboxamide (6a) via the immonium salt (4a):

Cyclohexanone (4.90 g, 50 mmol) and compound *(1)* (17.8 g, 110 mmol) are stirred under reflux in chloroform (60 ml) for 3 hours until *(1)* has dissolved completely and liberation of HCl has ceased. About half of the solvent is distilled off and a mixture of dry ether (40 ml) and pet. ether (10 ml) is added with stirring. The precipitated red oil *(4a)* crystallizes; the crystals are collected and washed thoroughly with dry ether. Yield 11.8 g (98%); m. p. 122—125 °C (decomp.) from $CHCl_3$; NMR spectrum ($CDCl_3$): δ (TMS = 0): 2.04 (4H,m), 2.80 (4H,m), 4.20 and 4.29 (6H,2 singlets).—Compound *(4a)* (6.7 g, 27.6 mmol) is stirred with H_2O (15 ml) and an excess of solid $NaHCO_3$. After 30 min, the mixture is extracted with CH_2Cl_2, dried with Na_2SO_4, and the solvent is evaporated off. The oily residue is distilled to give 3.70 g (71%) of *(6a)*. Compounds *(6b)* and *(6c)* can be prepared similarly.

Ethyl 2-(1-chloroethylidene)-N,N-dimethylmalonamate (11) and (4-chloro-6-dimethylamino-3-α-pyronyl)-N,N-dimethylcarboxamide (12):

Compound *(1)* (26.4 g, 0.163 mol) and ethyl acetoacetate (18.0 g, 0.138 mol) are refluxed in chloroform (150 ml) with stirring for 2 hours until a clear solution is obtained. The intermediate *(10)* is hydrolyzed with a suspension of $NaHCO_3$ in water. Distillation affords 7.5 g (27%) of *(11)*, b. p. 100/0.2 torr; NMR ($CDCl_3$): δ = 1.30 (3H,t), 2.63 (3H,s), 2.97 and 3.03 (6H,2 singlets), 4.25 ppm (2H,q, J = 7.5 Hz); IR (film): 1725, 1680, 1500, 1450, 1400, 1280, 1240, 1190, 1120, 1060, 1030 cm^{-1}.—*(12)* is prepared similarly from *(1)* (8.1 g, 50 mmol) and methyl acetoacetate (2.9 g, 25 mmol). The crude product is hydrolyzed, extracted with ether, and the residue is recrystallized from CCl_4. M. p. 150—151 °C, yield 1.1 g (20%); NMR ($CDCl_3$): δ = 3.11 (12H,s), 5.37 ppm (1H,s); IR ($CHCl_3$): 1713, 1630, 1600, 1532, 1411, 1097 cm^{-1}; UV (CH_2Cl_2): λ_{max} = 370 nm (ε = 33400); mass spectrum: 244 (M^+).

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[1] Immonium Chemistry, Part 3.—Part 2: *Z. Janousek* and *H. G. Viehe*, Angew. Chem. *83*, 615 (1971); Angew. Chem. internat. Edit. *10*, 574 (1971).

[2] *H. G. Viehe* and *Z. Janousek*, Angew. Chem. *83*, 614 (1971); Angew. Chem. internat. Edit. *10*, 573 (1971).

[3] *J. Žemlička* and *Z. Arnold*, Collect. Czech. Chem. Commun. *26*, 2838 (1961).

5-Ethoxy-1,2,3-trichloropentaleno[3,2,1-*cd*]-phenalene: A Perturbed [16]Annulene[1]

By *Ichiro Murata, Masaki Okazaki,* and *Tomoo Nakazawa*[*]

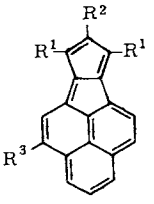
Recently, we reported the synthesis of 5-ethoxy-1,3-di-*tert*-butylpentaleno[3,2,1-*cd*]phenalene *(2)*, the first compound containing the pentalenophenalene skeleton *(1)*. Because of its properties we described *(2)* as a novel example of a peripheral 16 π electron model[2].

Our recent studies on 5-ethoxy-1,2,3-trichloropentaleno-[3,2,1-*cd*]phenalene *(3)*, which was obtained from 2-ethoxy-9,10,11,12-tetrachloropentaphenafulvalene *(4)*[3], support this view.

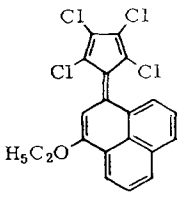
When a solution of *(4)* (0.438 mg) and a trace of triethylamine in chloroform (20 ml) was degassed, sealed under

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high vacuum, and kept at 30 °C, the color of the solution gradually turned from blue to wine red. The change can be followed spectrally, *i. e.*, it shows the gradual disappearance of *(4)* [λ_{max} = 410 and 608 nm] with simultaneous increase in absorbance at 552 nm [three isosbestic points at 385, 427, and 555 nm]. Preparative-scale reaction of *(4)* (60 mg) in chloroform (20 ml) in the presence of triethylamine (75 mg) under nitrogen at 30 °C for seven hours led to the isolation of *(3)* in 31% yield.



(1), $R^1 = R^2 = R^3 = H$

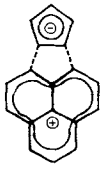


(4)

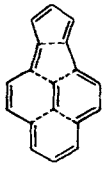
(2), $R^1 = t\text{-}C_4H_9$, $R^2 = H$, $R^3 = OC_2H_5$

(3), $R^1 = R^2 = Cl$, $R^3 = OC_2H_5$

After repeated chromatographic purification on basic alumina, compound *(3)* crystallized as unstable red prisms having no definite melting point. The new compound was characterized by elemental analysis and spectroscopy. Mass spectrum: $m/e = 372$ (M^+, 74%), 343 ($M-C_2H_5$, 100%). The presence of the pentalenophenalene skeleton *(1)* was inferred from the similarity of the IR spectrum (1640, 1590, 1560 cm^{-1}) to that of *(2)*[2]. UV spectrum: λ_{max} (cyclohexane) = 293 (log ε = 4.43), 307 (4.45), 319 (4.46), 360 (3.90, sh), 482 (3.95, sh), 512 (4.13), 542 (4.17), 584 nm (3.95); λ_{max} (acetonitrile) = 287, 304 (sh), 313, 370 (sh), 478 (sh), 518, 549, 597 nm. The NMR spectrum shows signals for the ethoxy group at δ = 1.36 (t, J = 7.0 Hz) and 3.95 ppm (q, J = 7.0 Hz), a singlet for H-4 at 5.01 ppm, an AB system (H-9, H-10) at 6.40 and 6.71 ppm (J = 8.0 Hz), and an AMX system (H-6, H-7, H-8) at 6.03, 6.82, and 6.53 ($J_{6,7}$ = 8.4 Hz, $J_{7,8}$ = 7.0 Hz)[4]. These values resemble those obtained for compound *(2)*[2] and for the perturbed [12]annulene, pyracylene[5]. Ring closure of *(4)* to give the pentacyclic *(3)* results in all the signals of the vinyl protons being shifted more than 1.5 ppm to higher field.



(5)



(6)

In 1958 *Reid* predicted the dipolar structure *(5)* for the hypothetical compound *(1)*[6]. The physical properties of our compounds *(2)* and *(3)*, *i.e.* slight solvatochromism in the electronic spectrum, relatively high chemical shifts of the protons on the phenalene nucleus, and small dipole moment [μ = 2.31 D in the case of *(2)*] indicate, however, that the ground state of these molecules are best represented by the perturbed [16]annulene *(6)* rather than the dipolar form *(5)*.

It is still undecided as to how the conversion of *(4)* into *(3)* actually takes place. According to orbital symmetry considerations, the thermally and the photochemically induced ring closure with participation of eight π electrons should proceed in a conrotatory and in a disrotatory fashion respectively. Our reaction can, in fact, be explained by this concept[7]; however, an ionic mechanism is both electronically and geometrically just as plausible[2]. Since the rate of transformation depends very strongly on the polarity of the solvent (at 30 °C in acetone: $t_{1/2} \approx 45$ min, in *n*-pentane: > 10 h), we favor the ionic mechanism. Furthermore, we have found that the allowed disrotatory ring closure does not take place in the photolysis of *(4)* at −78 °C.

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[1] Chemistry of the Phenalenium System, Part 5. — Part 4: *I. Murata, T. Nakazawa*, and *T. Tatsuoka*, Tetrahedron Lett. *1971*, 1789.

[2] *I. Murata, T. Nakazawa*, and *M. Okazaki*, Tetrahedron Lett. *1970*, 3269.

[3] *I. Murata, T. Nakazawa*, and *M. Okazaki*, Tetrahedron Lett. *1969*, 1921.

[4] A Varian HA 100 spectrometer fitted with Fourier transform pulse control was used for the recording of the NMR spectrum. We thank The Application Laboratory, Nippon Electric Varian Ltd., for carrying out the measurements.

[5] *B. M. Trost, G. M. Bright, C. Frihart*, and *D. Brittelli*, J. Amer. Chem. Soc. *93*, 737 (1971).

[6] *D. H. Reid*, Tetrahedron *3*, 339 (1958).

[7] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. Verlag Chemie, Weinheim 1970, p. 45.

Solvated Electrons in Liquid and Solid Solutions

The following report reviews the Discussion Meeting held by the Deutsche Bunsengesellschaft at Herrenalb (Germany) from March 29 to March 31, 1971.

The "solvated" or "stabilized" electron, regarded some time ago as a curiosity of metal-ammonia solutions, later recognized by radiation chemists familiar with the ways of short-lived species in other systems too, has won a firm place in the catalog of "interesting materials". The Discussion Meeting arranged by *U. Schindewolf* and *D. Schulte-Frohlinde*, attended by 86 participants from 13 countries and comprising about 30 introductory and short papers, provided an impressive review of the state and direction of investigations that have raised questions of interest equally to chemists and physicists.

Many of the papers were still concerned with the electrons in alkali-metal/ammonia solutions—apparently so readily accessible, yet whose various modes of occurrence are so difficult to study—where the main interest remains fundamentally in the transition from nonmetallic to metallic behavior in the liquid phase. In this transition, the concentration of electrons is relatively high, so optical-absorption and magnetic procedures fail, and other methods of investigation must be sought—thermoelectric measurements *(P. Damay, P. Chieux)*, dielectric behavior *(K. G. Breitschwerdt, H. Radscheit)*, reflection spectroscopy under pressure *(R. Vogelsgesang, U. Schindewolf)*, or ultrasound measurements and the influence of static pressure, which demonstrate the increase in compressibility of the "soft" electron solvates in ammonia over that of the solvent itself *(M. H. Parker, D. E. Bowen; K. W. Böddeker, R. Vogelsgesang)*.

It could be seen that the investigations are being extended in several directions. In spite of experimental difficulties, use will be made in the future of cesium solutions *(B. R. Dewald)* and, to a much greater extent than hitherto, of lithium solutions, so as to provide a better understanding of the influence of cations on the behavior of the dissolved electrons, a theme that stood out in many papers. Further effort is being directed toward the search for new solvents. In some cases it is possible to dissolve the alkali metals by addition of certain cyclic polyethers *(J. L. Dye, M. T. Lok, G. M. deBacker)*.

A fundamental limitation lies in the use of alkali metals. So other processes for producing solvated electrons are gaining in importance: electron field emission into aliphatic and aromatic hydrocarbons *(W. F. Schmidt, W. Schnabel)*, γ-irradiation of the ammono system *(J. Belloni)*, UV flash photolysis of dilute aqueous alkalis *(G. Kenney-Wallace, D. C. Walker)*, pulse radiolysis of the most varied solvent systems *(L. Dorfmann; N. Getoff, H. Lehmkuhl, F. Schwörer; U. Schindewolf)*, as well as supercritical ammonia, in which electrons can be recognized as "solvated" at solvent densities down to 0.1 g/ml at 150°C *(R. Olinger, U. Schindewolf)*. It is still an open question whether electrons acquire a temporary "hydrated" state during electrolysis of aqueous solutions—there cannot be many that do *(D. C. Walker; D. Postl, U. Schindewolf)*.

Since the concentration of electrons in all non-ammoniacal solvents is small (mostly $<10^{-4}$ mol/l) and their lifetime is short, absorption spectra still play the largest role in the study of these solutions *(F. S. Dainton; L. Dorfman)*. Laser excitation has been used in attempts to "manipulate" the absorbing electrons *(G. Kenney-Wallace, D. C. Walker)* or to influence their subsequent reactions *(G. C. Barker)*. Meanwhile, the nonmetal/metal transition observed when supercritical metal vapors are compressed can also be followed by optical methods *(F. Hensel)*.

The production of electrons by radiation-chemical methods, and their investigation in frozen and particularly such aqueous solutions, have naturally attracted much attention since, after some guesswork, the occurrence of "hydrated" electrons has been finally proved in such systems *(K. Eiben, D. Schulte-Frohlinde; J. Jortner)*. The studies were concerned with the nature of added or radiation-induced "trapping sites" *(J. J. Weiss)*, with luminescence phenomena *(M. Magat; J. Moan)*, and with the chemical reactivity to electron scavengers which provides information about, *inter alia*, the mobile "dry" electrons before they are solvated, *i.e.*, before they can be detected optically *(K. Eiben, H. Wieczorek; H. B. Steen)*. Electrons trapped in the anion vacancies of ionic crystals (F centers) find themselves in a relatively well-ordered environment, which can be traced through several crystal layers by the hyperfine structure of ENDOR spectra *(H. Seidel)*.

The depth to which the solvated electron has penetrated into chemical studies is illustrated by the fact that "applications" are already being discussed, for instance, for clarification of complicated reductive reactions *(A. Henglein)*. Other papers were concerned with pulse-radiolytic or radiation-chemical reactions with halogenated hydrocarbons *(R. Köster, K.-D. Asmus)*, with carboxylic acids *(O. Mićić, V. Marković)*, with transition-metal complexes *(I. G. Murgulescu, J. Paun)* in aqueous solution, and with organoaluminum compounds in ether *(N. Getoff, H. Lehmkuhl, F. Schwörer)*. Also reactions of metal-ammonia and metal-amine solutions with water and alcohols have been studied kinetically *(R. R. Dewald)*.

Whereas experimentalists may perhaps find it difficult to comprehend the nonmetal/metal transition, theory approaches the convenient "cavity model" for solvated electrons with mistrust. So far as liquid solutions are concerned it is only in ammonia that the electron appears to be strictly localized in the cavities suggested by the measureable increase in volume, whereas in water, for instance, the charge is distributed over wide areas *(G. Howat, B. C. Webster)*. The extraordinary stability of the electron dissolved in ammonia is rationalized by its abnormally high entropy, which enters the rate constants of the reactions—including decomposition—as an important factor alongside the activation energy *(G. Lepoutre, A. Demortier)*; the relation between the activation entropy and the activation volume here leads back to the cavity concept *(R. Olinger, U. Schindewolf)*. The detailed studies of conditions required for existence of excess electrons in polar and nonpolar liquids *(J. Jortner)*, extension of the polaron theory *(V. Shubin)*, and the theory of charge-transfer processes in polar media *(R. Dogonadze)* will refine the concepts and doubtless provide stimulus for further experimentation.

A special feature of this Discussion Meeting was the open-minded relation between theory and practice that proved to be of mutual stimulation to the participating radiation chemists and physical chemists and of metal and solid-state physicists.

K. W. Böddeker [VB 302 IE]
German version: Angew. Chem. *83*, 590 (1971)

Stereochemistry of Macromolecules

By *Rolf C. Schulz*[*]

The shape of a macromolecule depends mainly on the structure and arrangement of the monomeric units, as well as on the experimental conditions. The stereochemical problems discussed in this lecture referred therefore principally to the primary structure.

The concept of tacticity introduced by *Natta* is generally applied only to sterically ordered polyvinyl compounds, but it can be shown that this concept is also applicable to polycondensates (in general, heterochain polymers). A prerequisite for appearance of tacticity is that each monomeric unit shall contain at least one center of stereoisomerism. In polyvinyl compounds such centers may be carbon atoms of the main chain bearing two different substituents or C=C double bonds. In addition, any chiral group that can be built into the main chain can give rise to tactic arrangements. Heterochain polymers thus offer a variety of possibilities.

Simple examples are polyethers, polyamides, and polyesters with asymmetric carbon atoms in the main chain, for example, polypropylene oxide, poly-α-amino acids, polyesters of lactic, 3-hydroxypropionic, and tartaric acids, *etc.* In contrast to isotactic polyvinyl compounds, isotactic heterochain polymers are optically active. Polyamides and polyurethanes have been described that contain atropisomeric biphenyl or binaphthalene groups in place of asymmetric carbon atoms and can thus occur in isotactic forms. Some become atactic on thermal isomerization. Further, several *all-trans*-polyazo compounds have been prepared; and these constitute a further type of sterically ordered and thus tactic polymer; they can be partially converted into the *cis*-isomers by irradiation. Further, some examples of polyesters of *cis*- and *trans*-cyclopropanedicarboxylic acid and some spiro compounds have been described.

Lecture at Freiburg on May 17, 1971 [VB 301 IE]
German version: Angew. Chem. *83*, 590 (1971)

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The Base-Catalyzed Halogen Dance

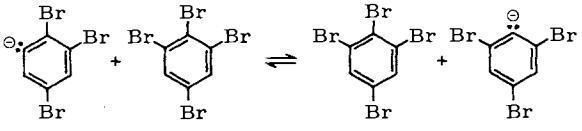
By *Joseph F. Bunnett*[*]

On treatment with potassium anilide in liquid ammonia, 1,2,4-tribromobenzene rearranges to its 1,3,5 isomer. When the hydrogen positions are fully deuterated, both the 1,3,5- and the recovered 1,2,4-tribromobenzene are obtained deuterium-free. When the 1-position is initially labeled with radioactive bromine, the recovered 1,2,4-tribromobenzene has the radiolabel equally distributed among the 1-, 2-, and 4-positions.

1,3-Dibromo-4-iodobenzene, when exposed to potassium anilide in liquid ammonia, affords its 1,3,5-isomer as well as 1,2,4-tribromobenzene and 1-bromo-3,5-diiodobenzene.

Isomerization of 1,2,4-tribromobenzene is also catalyzed by potassium *tert*-butoxide in DMF. However, neither with this reagent in DMF nor with potassium anilide in liquid ammonia does 1,3,5-tribromobenzene revert to its 1,2,4-isomer. On the other hand, reversion does occur if 1,2,3,5-tetrabromobenzene is supplied as co-catalyst, and the same equilibrium proportions of 1,2,4- and 1,3,5-tribromobenzene are obtained starting from either compound. The tetrabromobenzene does not need to be added in order to co-catalyze rearrangement of 1,2,4-tribromobenzene because it is generated in the reaction mixture by disproportionation.

The requirement for tetrabromobenzene co-catalyst rules out any reaction mechanism which does not assign an essential role to the tetrabromobenzene. Specifically, a conceivable aryne mechanism and a mechanism (for isomerization) of 1,2-shifts in *o*-halophenyl anions are rejected. A mechanism which does accommodate all the experimental evidence is one involving reversible acid-base reactions to form *o*-halophenyl anions *(1)* and the attack by such anions on halogen of a tetrahalobenzene *(2)*, so as to capture a positive halogen entity[1].



(1) *(2)*

Lecture at Münster on April 26, 1971 [VB 303 IE]
German version: Angew. Chem. *83*, 590 (1971)

[1] *J. F. Bunnett et al.*, J. Amer. Chem. Soc. *93*, 1183, 1190, 1198, 1201 (1971).

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Mechanism and Application of Anionic Lactam Polymerization

By *Georg Falkenstein*[*]

Mono- and di-substituted carbamoyl lactams and *N*-lactamcarboxylic esters are recognized as particularly effective activators of anionic lactam polymerization.

It has been found that activated anionic lactam polymerization occurs largely by nucleophilic polyaddition of lactam anions to the endocyclic carbonyl-carbon atom of the temporarily terminal acyl lactam ring. This explains also the effect of the cited activators; they replace the first polymerization member, *N*-ε-aminocarbamoyllactam, which would otherwise be formed relatively slowly and secondarily from lactam anions and lactam; and in this way they bring about chain growth.

Possibilities for optimization of the activator efficiency were demonstrated on simple models. Guide lines are provided by the Hammett substitution constants, the pK_B values of the carbamoyl-nitrogen atom of the disubstituted carbamoyl lactams, and the absorption bands of the exocyclic carbonyl groups of the *N*-lactamcarboxylic esters or monosubstituted carbamoyl lactams. Activators can thus be prepared "to measure", which is of great interest for the various types of polymerization process. The polymerizates obtained in the presence of the new activators show particularly favorable mechanical properties.

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The considerable amount of research already carried out in industry and Institutes in the field of anionic lactam polymerization contrasts with the, so far, relatively modest application in practice.

At present, the most important processes are: (i) pressureless casting of shaped parts and semifinished products similar to metal casting; (ii) centrifugal casting for the manufacture of rotationally symmetrical parts, in which the mold is rotated about an axis in order to utilize the resulting centrifugal force; and (iii) rotational casting for the manufacture of hollow parts using a two-axis principle in which the axes are at 90° to each other.

Lecture at Aachen on March 19, 1971 [VB 304 IE]
German version: Angew. Chem. *83*, 624 (1971)

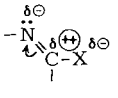
Chemistry of Reactive Dyes

By *Edgar Siegel*[*]

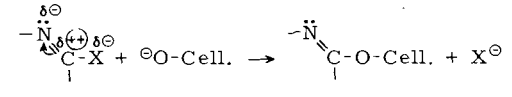
In 1954 *Rattee* and *Stephen* discovered that cellulose reacts with dichloro-*s*-triazine dyes in dilute aqueous alkaline solution in technically interesting yields without hydrolysis of the main amount of the dissolved dye. Since then more than 40 ranges of reactive dyes have come on the market.

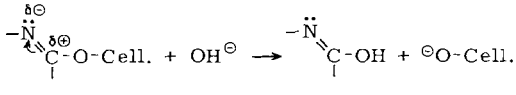
The mono- and di-chloro-*s*-triazine, trichloropyrimidine, 2,3-dichloro-6-quinoxalinecarbonyl, and β-sulfatoethyl sulfone dyes, which are still important today, have been supplemented during the last five years by a series of new systems.

The main object of the new developments was higher reactivity of the dye with cellulose, combined with greater stability, that is, lower reactivity at the fiber-dye bond that is formed. This purpose was achieved by use of leaving groups that are more electronegative than chlorine, thus causing temporary activation at the electrophilic C atom which disappears along with the leaving group (HO-Cell. = cellulose).



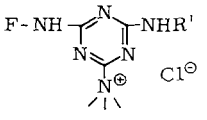
δ⊕ for X = F > $\overset{\oplus}{N}R^1R^2R^3\ Cl^{\ominus}$ > SO_2R > Cl

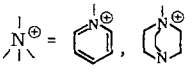




New reactive systems based on this principle bear the following substituents introduced into amino-group containing dyes: 5-chloro-2,4-difluoro-pyrimidylamino [Levafix® P-A, Levafix® E-A, Verofix® (Bayer); Drimaren® R, Drimalan® F (Sandoz)]; 5-chloro-2-methanesulfonyl-4-methylpyrimidylamino [Levafix® P (Bayer)], and β-(2,2,3,3-tetrafluorocyclobutyl)acryloylamino (Hoechst).

In this connection, mention should also be made of the monochloro-*s*-triazine dyes whose reactions are catalyzed by tertiary amines; the annexed formulas show dyes with attached catalyst (ICI, CIBA).





Further, increased reactivity has been achieved in a conventional manner, *i.e.*, without temporary activitation, by introducing the following groups: 2-chloro-4-methoxy-*s*-triazinylamino [Cibacron Pront® (Ciba-Geigy)] or 2,4-dichloro-5-pyrimidinecarbonylamino [Reactofil® (Ciba-Geigy)].

Dyes have also been introduced with two or more monochloro-*s*-triazinylamino groups in the molecule [Procion® Supra (ICI)].

In the Calcobound dyes of American Cyanamide cellulose is combined with groups that react in acid solution, namely, *N*-hydroxymethylmelamine groups. 2-Bromoacryloylamino [Lanasol® (Ciba-Geigy)] and 5-chloro-2,4-difluoropyrimidylamino dyes (Verofix, Drimalan R) are the first to allow dyeing of wool with fixation yields of more than 85–90% and thus in a technically satisfactory manner.

Lecture at Tübingen on April 23, 1971 [VB 305 IE]
German version: Angew. Chem. *83*, 624 (1971)

Extraction of Transplutonium Elements by Alkylammonium Salts

By *Werner Müller*[*]

Alkyl-substituted ammonium salts are used for extraction of trivalent transplutonium elements from concentrated chloride or nitrate solutions[1].

In organic solution the alkylammonium salts exist mainly as ion pairs; their formation constants increase with the strength of the acid and the polarity of the diluent. Polar diluents stabilize the ion pairs, which can dissociate in very dilute solution. The weak solvation by nonpolar diluents causes self-association of the alkylammonium salts in concentrated solution and enhances the extraction of hydrate water and excess of acid into the organic phase. Correspondingly, extraction of the metal complexes is increased if a polar diluent such as chloroform is replaced by an alkylbenzene or cyclohexane.

On extraction of trivalent transplutonium elements from weakly acid, highly concentrated chloride solutions by tridodecylammonium chloride, ion pairs $R_3NH^+MCl_4^-$ are formed, which may be associated with additional molecules of the extractant. The differing strengths of these complexes permit separation of the element pairs Cf-Es and Am-Cm as well as their separation from the trivalent lanthanides. Am and Cm can be separated from each other by extraction from lithium nitrate solution by quaternary alkylammonium nitrates.

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Extraction chromatography by tridecylmethylammonium nitrate on kieselguhr as carrier, which was previously used for purification of Am and Cm in milligram amounts[2, 3], has now been extended successfully to the separation and purification of ^{241}Am, ^{243}Am, and ^{244}Cm in multigram quantities[4].

Lecture at Saarbrücken on May 7, 1971 [VB 307 IE]
German version: Angew. Chem. *83*, 625 (1971)

[1] *W. Müller*, Actinides Rev. *1*, 71 (1967).

[2] *E. P. Horwitz, C. A. A. Bloomquist, K. A. Orlandini*, and *D. J. Henderson*, Radiochim. Acta *8*, 127 (1967).

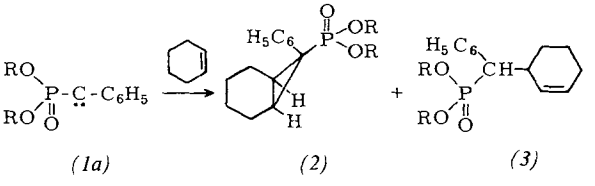
[3] *W. Müller, F. Maino*, and *J. Cl. Toussaint*, EUR 4409e (1970).

[4] *K. Buijs, F. Maino, W. Müller, J. Reul*, and *J. Cl. Toussaint*, to be published.

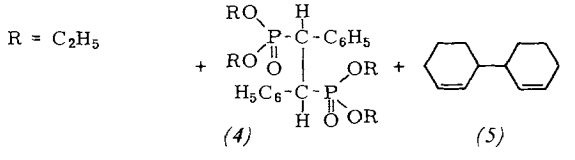
PO-Substituted Carbenes

By *Manfred Regitz, Hans Scherer*, and *Annemarie Liedhegener*[*]

Carbenes containing $OP(OR)_2$ or OPR_2 groups have been produced by photolysis of correspondingly substituted diazo compounds. The former type of carbene shows pronounced triplet reactivity: Treatment of *(1a)* with cyclohexene gives, besides the norcarane *(2)*, the abstraction products *(3)*, *(4)*, and *(5)*. The reaction with *p*-xylene as H-donor occurs in a similar sense (no norcaradiene is formed!). Also, *cis*- and *trans*-butene are cyclopropanated non-stereospecifically.

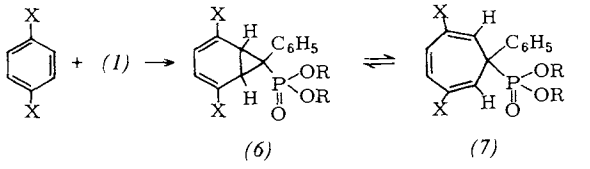


(1a) *(2)* *(3)*



(4) *(5)*

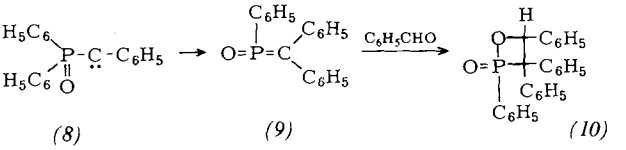
With benzene or substituted benzenes the carbenes *(1)* yield 1:1 adducts. The problem of their structure—whether of norcaradiene *(6)* or cycloheptatriene type *(7)* or a valence-tautomeric equilibrium *(6)*⇄*(7)*—was decided for series *(b)* in favor of the equilibrium on the basis of the temperature-dependent ^{1}H-NMR spectra[1]; the same is true for the series *(c)* and *(d)*. However, the cyclopropanation product of 1,4-dichloro- and 1,4-dimethoxy-benzene appears to be the homogeneous norcaradiene *(6e)* or *(6f)*, respectively, with an *exo*-PO group ($^3J_{H,P} \approx 16$ Hz)[1].



(6) *(7)*

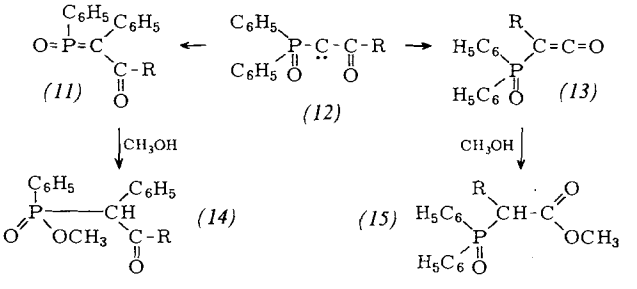
(b) X = H, R = CH_3; *(c)* X = H, R = C_2H_5; *(d)* X = H, R = iso-C_3H_7; *(e)* X = Cl, R = CH_3; *(f)* X = OCH_3, R = CH_3.

The reactivity of carbenes containing OPR_2 groups is expressed preponderatingly by their tendency to rearrange. Thus *(8)* passes into the methyleneoxophosphorane *(9)* by *P/C*-phenyl migration, and the product can be trapped by benzaldehyde which leads to formation of the 1,2-oxaphosphetane *(10)*.



(8) *(9)* *(10)*

Acylcarbenes *(12)* containing OPR_2 groups undergo competing rearrangements (*P/C*-phenyl or *C/C*-R migration) to the heterocumulenes *(11)* and *(13)*, which in methanol react further to afford the esters *(14)* and *(15)*. Reductive elimination of N_2 from the parent diazo compounds and OH insertion into the carbenes are side reactions.



(11) *(12)* *(13)*

(14) *(15)*

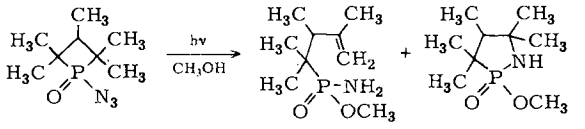
R = CH_3, C_6H_5, or *p*-X-C_6H_4;
X = Br, OCH_3, $N(CH_3)_2$, or NO_2.

Lecture at Mainz on April 29, 1971 [VB 306 IE]
German version: Angew. Chem. *83*, 625 (1971)

[1] *H. Gunther, B. Tunggal, M. Regitz, H. Scherer*, and *F. Keller*, Angew. Chem. *83*, 585 (1971); Angew. Chem. internat. Edit. *10*, 563 (1971).

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Photolysis of 1-azidophosphetane 1-oxides such as *(1)* leads, according to a report by *M. J. P. Harger*, to products whose formation results from loss of nitrogen and ring opening [*(2)*] or ring expansion [*(3)*]. Photolysis of 1-azido-2,2,4,4-tetramethyl-phosphetane 1-oxide gave, as

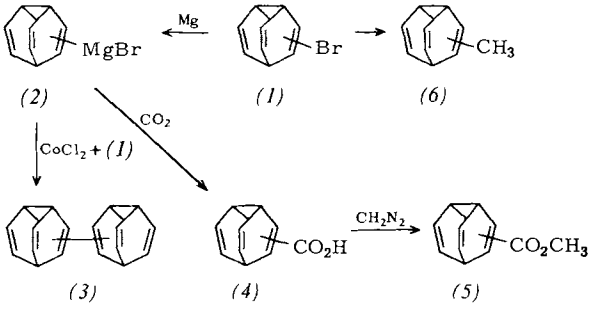


(1) *(2)* *(3)*

expected, two isomeric products of ring expansion in approximately equal amounts along with the open-chain compound. / Chem. Commun. *1971*, 442 / –Ee.

[Rd 362 IE]

Molecules with fluctuating bonds have been studied, primarily on the basis of their temperature-dependent spectra, by *J. F. M. Oth, E. Machens, H. Röttele*, and *G. Schröder*. The bibullvalenyl *(3)*, the bullvalenecarboxylic acid *(4)*, and its methyl ester *(5)* are obtainable from the bromobullvalene *(1)* by way of the Grignard compound *(2)*. Methylbullvalene *(6)* is prepared directly from *(1)* and

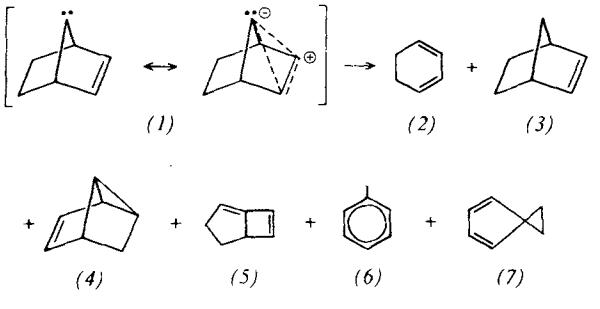


(2) *(1)* *(6)* *(3)* *(4)* *(5)*

methylmagnesium iodide in the presence of $CoCl_2$. In the case of bibullvalenyl *(3)* only the three isomers bound *via* the olefin groups are to be found in the equilibrium mixture. Isomers in which the substituents belong to an olefinic grouping also predominate in the case of the monosubstitution products *(2)* and *(4)*—*(6)*. / Liebigs Ann. Chem. *745*, 12 (1971) / –Ee.

[Rd 363 IE]

7-Norbornenylidene *(1)*, a potentially nonclassical carbene, occurs, according to a report by *R. A. Moss, U.-H. Dolling*, and *J. R. Whittle*, in the pyrolysis of the lithium salt of 7-norbornenone tosylhydrazone at 190—191 °C/0.05 torr.



(1) *(2)* *(3)* *(4)* *(5)* *(6)* *(7)*

The carbene decomposes mainly to the products *(2)* to *(7)*, compound *(5)* being present in about 67% yield (based on the sum of all products). / Tetrahedron Lett. *1971*, 931 / –Ee.

[Rd 367 IE]

Charge-transfer bands of amine-aromatic hydrocarbon complexes could be detected in absorption by *H. Ishida* and *H. Tsubomura*. Until now, only the fluorescence of these complexes (at about 500 nm) was known, from solutions of, *e.g.*, anthracene and tri-*n*-butylamine in *n*-hexane. The corresponding absorption bands were obscured by the strong absorption of amines in the corresponding spectral region (250—280 nm). In the adsorbed state, these absorption bands could be measured: spectra were recorded of thin layers of silica gel on which anthracene and amine had been adsorbed. With this system, however, no fluorescence is found. This can be rationalized in terms of the large Stokes shift between absorption and fluorescence maxima: this large shift is due to a considerable change of nuclear coordinates between the lowest vibrational levels of ground state and excited state. In the adsorbed complex the relaxation process that normally populates the lowest vibrational level of the excited state is strongly perturbed. Therefore, no fluorescence is observed. / Chem. Phys. Lett. *9*, 296 (1971) / –Hz.

[Rd 372 IE]

The photochemistry of piperidinoanthraquinones is reported by *A. K. Davies, J. F. McKellar*, and *G. O. Phillips*, and its relevance to phototendering of fabrics by related anthraquinonoid vat dyes. The dependence of electronic spectra on the dielectric constants of solvents shows that the longest wavelength absorption of the unprotonated forms of these compounds is due to an intramolecular charge transfer (CT). On acidification, the CT band of 1-piperidinoanthraquinone (1-PAQ) disappears; the lowest energy absorption is now a shoulder at about 400 nm of $n \rightarrow \pi^*$ character. In this excited state, 1-PAQ is a strong hydrogen abstracting agent with respect to H donors as, *e.g.*, cellulose. In an alkaline medium, the photolysis of 1-PAQ finally forms the dianion; 2-PAQ, however, is converted into the relatively stable radical anion (semiquinone). / Proc. Roy. Soc. *A 323*, 69 (1971) / –Hz.

[Rd 373 IE]

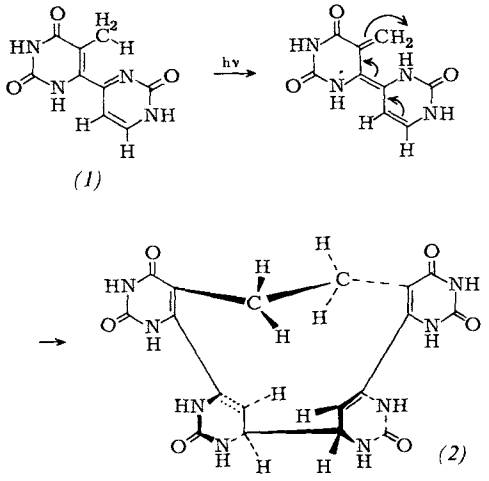
Gaseous mixtures of $AlCl_3/Al_2Cl_6$ and $NaAlCl_4$ are electrical conductors, as has been shown by *E. W. Dewing*. The conductances were measured in a concentric electrode arrangement, end currents being eliminated by measurements with the central electrode displaced in an axial direction. At 500—900 °C values of 10^{-11} to 10^{-6} ohm^{-1} cm^{-1} were measured. From the dependence of conductance on temperature, total pressure, and $NaAlCl_4$ partial pressure the author concludes that the conductivity is due to the ionization process

$$NaAlCl_4 + AlCl_3 = NaAlCl_3^+ + AlCl_4^-$$

This reaction is endothermic with $\Delta H \approx 70$ kcal mol^{-1}. The results are not consistent with Na^+, $NaAl_2Cl_6^+$, $Na_2AlCl_4^+$, or Na_2Cl^+ being the positive ions participating in the conduction process. / J. Phys. Chem. *75*, 1260 (1971) / –Hz.

[Rd 374 IE]

A pyrimidine phototetramer is described by *S. Yi Wang* and *D. F. Roades*. Compound *(2)* was obtained in 55% yield on irradiating an aqueous solution of 4-(2-oxo-1,2-dihydro-4-pyrimidyl)thymine *(1)* with 360-nm light. Previously, *(1)* has been prepared from acid hydrolyzates of

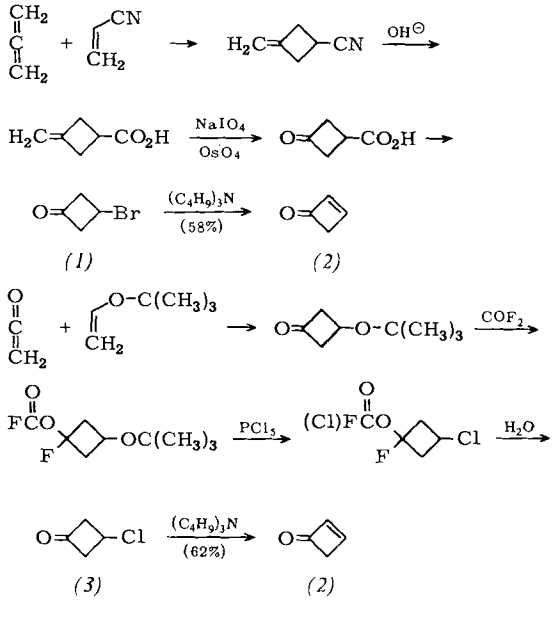


(1) *(2)*

UV irradiated DNA as well as by irradiation of a uracil/thymine mixture in the frozen state. *(2)* is formed by head-to-head and tail-to-tail dimerization of *(1)*. The conformation of the dimer was determined x-ray crystallographically using single crystals. Similar photoreactions as in the formation of *(2)* (H withdrawal at thymine CH_3 groups) could also occur during irradiation of the DNA. / J. Amer. Chem. Soc. *93*, 2554 (1971) / –Ma.

[Rd 375 IE]

The synthesis of cyclobutenone *(2)* from 3-bromo- or 3-chlorocyclobutenone [*(1)* or *(3)*] has been accomplished for the first time by *J. B. Sieja*. *(1)* and *(3)* were prepared from allenes and ketones. Cyclobutenone *(2)*, whose structure could be confirmed by IR, UV, and mass spectrometry, rapidly polymerizes. Even at −78 °C considerable

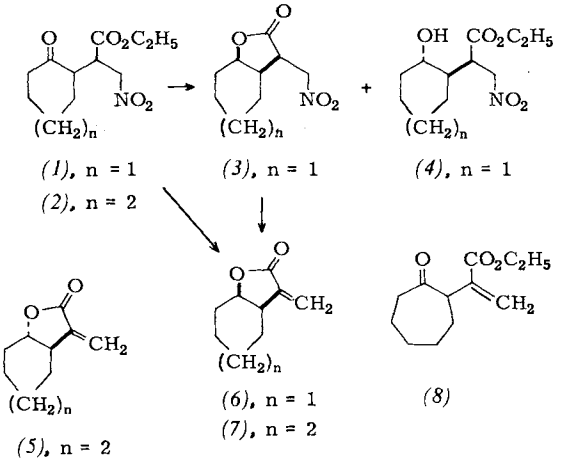


(1) *(2)* *(3)* *(2)*

polymerization takes place within 12 h. / J. Amer. Chem. Soc. *93*, 2481 (1971) / –Ma.

[Rd 376 IE]

A new synthesis of α-methylenebutyrolactones reported by *J. W. Patterson* and *J. E. McMurry* proceeds in three steps: 1. enamine formation, 2. Michael addition of ethyl β-nitroacrylate, and 3. reduction with $NaBH_4$ and simultaneous lactonization and elimination of the nitro group. The morpholine enamine of cyclohexanone adds to ethyl β-

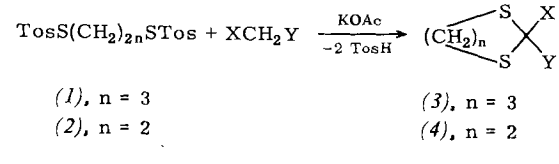


(1), n = 1 *(3)*, n = 1 *(4)*, n = 1
(2), n = 2
(5), n = 2 *(6)*, n = 1 *(8)*
(7), n = 2

nitroacrylate to give the adduct *(1)* (81% yield after hydrolysis). Reduction of *(1)* with $NaBH_4$ in methanol (1 h, 0 °C) affords, in almost quantitative yield, a 50:50 mixture of *cis*-nitromethyllactone *(3)* and *trans*-hydroxy ester *(4)*. On treatment with one equivalent of diisopropylamine (in $CHCl_3$, room temperature), *(3)* is converted into the *cis*-α-methylenebutyrolactone *(6)*. The morpholine enamine of cycloheptanone gives the adduct *(2)* (49%) and the elimination product *(8)* (21%); reduction of *(2)* with $NaBH_4$ gave an 86:14 mixture of *cis*- and *trans*-α-methylbutyrolactone *(5)* and *(7)* (91%). / Chem. Commun. *1971*, 488 / –Ma.

[Rd 378 IE]

Dithiotosylates as reagents in organic synthesis are reported by *R. B. Woodward*, *I. J. Pachter*, and *M. L. Scheinbaum*. Trimethylene- and ethylene dithiotosylate, *(1)* and *(2)*, react with activated methylene groups to give 2,2-substituted 1,3-dithianes *(3)* and 1,3-dithiolanes *(4)* respectively. The dithioketal groups of *(3)* and *(4)*, unlike the acetal



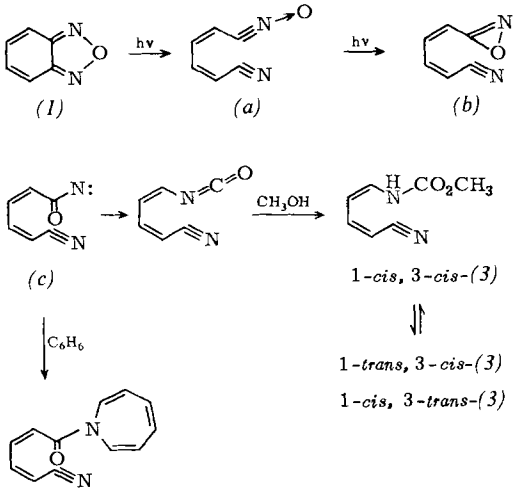
(1), n = 3 *(3)*, n = 3
(2), n = 2 *(4)*, n = 2

groups of the analogous oxygen compounds, are remarkably acid stable and consequently further rearrangements of such protected methylene compounds are possible even in an acid medium. The methylene group can be regenerated by Raney nickel reduction, and converted into a carbonyl group by Hg^{2+}-catalyzed hydrolysis. Carbonyl compounds having less reactive CH_2 groups can be activated by conversion into an enamine or an hydroxymethylene derivative prior to reaction with *(1)* or *(2)*. Reliable methods were developed for the preparation of *(1)* and *(2)*. / J. Org. Chem. *36*, 1137 (1971) / –Ma.

[Rd 379 IE]

The photochemistry of benzofurazane has been investigated by *M. Georgarakis*, *H. J. Rosenkranz*, and *H. Schmid*.

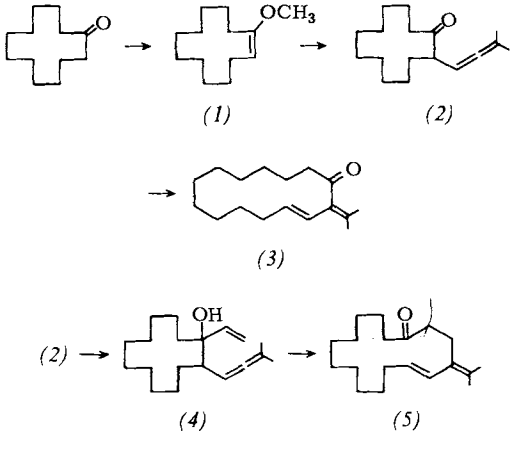
Irradiation of *(1)* in benzene (8×10^{-3} mol/l, 10—12 °C, argon, Hg high-pressure vapor lamp) gives the azepin derivative 2-*cis*,4-*cis*-5-cyano-2,4-pentadiene *(2)* as the main product (16%). Subsequent addition of methanol in the dark leads to additional formation of the 1-*cis*,3-*cis* form of methyl *N*-(4-cyano-1,3-butadien-1-yl)carbamate *(3)*. Irradiation of *(1)* in methanol leads to a mixture of



the stereoisomeric forms of *(3)* (18%), from which the pure 1-*trans*,3-*cis* isomers can be obtained. The reaction products are formed *via* the nonisolable reactive intermediates *(a)*, *(b)*, and *(c)* (nitrene). / Helv. Chem. Acta *54*, 819 (1971) / –Ma.

[Rd 380 IE]

The ring expansion of cyclododecanone by two and four carbon atoms is described by *R. C. Cookson* and *P. Singh*. Condensation of 1-methoxy-1-cyclododecene *(1)* with 2-methyl-3-butyn-2-ol yields, through a Cope rearrangement of the intermediate enol ether, 2-(3,3-dimethylallenyl)-cyclododecanone *(2)*. On UV irradiation *(2)* isomerizes with 1,3-acyl migration to give *(3)*, from which 2-isopropyl-cyclotetradecanone can be obtained by hydrogenation. The alcohol *(4)*, obtained from *(2)* by addition of vinyl-



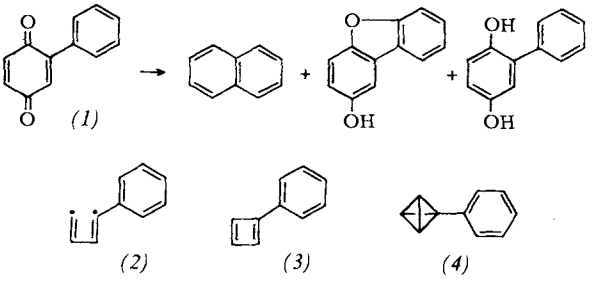
magnesium bromide, is converted by thermal Cope rearrangement into the compound *(5)*. / J. Chem. Soc. *C 1971*, 1477 / –Ma.

[Rd 381 IE]

Novel fluorides of divalent palladium have been prepared by *B. Müller* and *R. Hoppe*. Pure PdF_2 (bright violet) was obtained for the first time from mixtures of Pd/PdF_3 at 500—750 °C in F_2/Ar. The fluoro complexes $M^{II}[PdF_4]$, M = Ca, Sr, Cd, Pb, Ba, could be prepared from mixtures of $MF_2 + PdF_2$ (700 °C, closed system) as well as by thermal degradation of $M^{II}PdF_6$ (750 °C, Ar). These tetrafluoropalladates belong to the tetragonal $K[AuF_4]$-type compounds. $CaPdF_4$ is crimson, $SrPdF_4$ carmine, $CdPdF_4$ blue, $PbPdF_4$ crimson, and $BaPdF_4$ (impure) and Ba_2PdF_6 are orange-red. / Naturwissenschaften *58*, 268 (1971) / –Ma.

[Rd 382 IE]

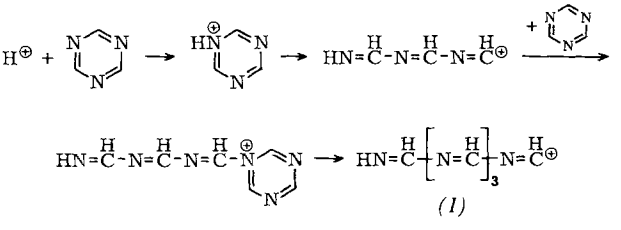
The flash-vacuum thermolysis of phenyl-*p*-benzoquinone *(1)* has been investigated by *H. J. Hageman* and *U. E. Wiersum*. At 800 °C, three major products were observed: naphthalene (54 mol-%), 2-hydroxydibenzofuran (8%), and phenyl-1,4-hydroquinone (*ca.* 8%) [conversion of *(1)* *ca.* 60%]. The formation of naphthalene can be interpreted as an intramolecular trapping of either a butadiene diradical *(2)*, cyclobutadiene *(3)*, or tetrahedrane derivative *(4)* by the phenyl ring. A similar behavior was observed for several



substituted phenyl-*p*-benzoquinones. / Chem. Commun. *1971*, 497 / –Ma.

[Rd 383 IE]

Poly(methinimine), polynitrile *(1)* has been prepared for the first time by *D. Wöhrle* by thermally induced ring-opening of 1,3,5-triazine-zinc chloride complexes under N_2 at 200—350 °C. The polymeric mixture formed in 10—60% yield is purified by extraction with acetone and reprecipitation from H_2SO_4. The IR spectra show characteristic bands at 3170 cm^{-1} (CH stretching vibration). It is assumed that an initially occurring proton-donating complex from Lewis acis ($ZnCl_2$) and cocatalyst (1,3,5-triazine or HPO_3) triggers the ring cleavage to the polymer



having a polymethinimine structure. / Tetrahedron Lett. *1971*, 1969 / –Ma.

[Rd 384 IE]

Chemische Elementaranalyse mit kleinsten Proben (Elemental Chemical Analysis with Very Small Samples). By *G. Tölg*. Verlag Chemie, Weinheim 1967. 1st Ed., viii, 228 pp., 66 figs., 5 tab. bound, DM 32.—.

The development of elemental organic analysis is strongly influenced by the needs of biology, biochemistry, and medicine, and this means that the amount of substance required is tending to become smaller and smaller. The author, an international expert in this field, presents an excellent review of the current achievements, including descriptions of procedures requiring only a few micrograms (in some cases only a few nanograms) of the elements to be determined.

The book is divided into two parts. The first is a general section, and is concerned with the basic principles of handling such small quantities—weighing, measuring, transferring—and the appropriate safety precautions, together with the equipment, relating these topics as closely as possible to practical needs. The second, more specific part gives methods for the determination of carbon, hydrogen, oxygen, nitrogen, sulfur, fluorine, chlorine, bromine, iodine, phosphorus, and arsenic. Several reliable methods are given in each case, which is particularly important for ultramicroanalysis. It is gratifying to find that many of the methods are characterized by their standard deviation. Special attention is paid to titrimetric procedures (usually in combination with electrical indication) and photometric techniques. Most of the methods, which, incidentally, are all described with a refreshing degree of clarity, are accompanied by descriptions and illustrations of equipment specifically intended for the purpose. This book is a valuable addition to the literature devoted to analysis, and is heartily recommended.

Günther Kraft [NB 976 IE]

Neuere Methoden der Präparativen Organischen Chemie (Newer Methods of Preparative Organic Chemistry). Edited by *W. Foerst*. Verlag Chemie, Weinheim 1970. Vol. 6, vi, 297 pp., 3 figs., 60 tab., bound, DM 38.—.

This is the last volume of a series begun in 1944. It contains ten articles (in most cases considerably expanded) from Angewandte Chemie on the following topics (the date at the end of each reference is the year in which the article appeared in Angewandte Chemie):

Preparation, properties, and reactions of polychloroamine derivatives (*H. Holtschmidt et al.*, 1968),

Directed aldol condensations (*H. Reiff*, 1968),

Carboxylic acid syntheses from 1,1-dichloroethylene (*K. Bott* and *H. Hellmann*, 1966),

Diazo group transfer (*M. Regitz*, 1967),

Isocyanide dihalide syntheses (*E. Kühle*, *B. Anders*, and *G. Zumach*, 1967, 1969),

Synthesis and reactions of cyanic esters (*E. Grigat* and *R. Pütter*, 1967),

Ring closure reactions with carbon monoxide (*J. Falbe*, 1966),

Synthesis of isocyanates and carbodiimides (*H. Ulrich* and *A. A. R. Sayigh*, 1966),

Additions to the activated C—C triple bond (*E. Winterfeldt*, 1967),

s-Triazine derivatives by polar cycloaddition of isocyanates (*H. Ulrich* and *R. Richter*).

Each chapter contains numerous descriptions of preparations, which are thorough enough to make reference to the original literature unnecessary. It is hardly necessary to emphasize here the other advantages and the usefulness of this collection to all preparative chemists, university lecturers, and students, since this was done quite adequately in the reviews of Volumes IV and V[1]. As with the previous issues, this new volume can be recommended without reservation.

There is an underlying note of sadness in the editor's introduction, as though he were bidding farewell to a class of reader who is rapidly becoming extinct. In this he is only partly justified. Certainly there is a decreasing tendency, particularly among the younger generation of chemists, to have one's own personal copy of the essential literature to be kept at home on the bedside table, and there is an increasing tendency to expect the company or the state to pay for everything. But, evidently, this does not influence the intensity of research, since there is no decrease in the number of papers published in journals or monographs. Indeed, there is a journal devoted to synthesis alone. The style and the objectives of the research are changing, and we shall have to tread new paths if we are to keep fully abreast of new developments. Over the past 25 years, *Foerst*'s "Neuere Methoden" have played an important part in this endeavor. It is about time to devote some thought to the next 25 years.

Hans Musso [NB 977 IE]

[1] Cf. Angew. Chem. internat. Edit. 7, 83 (1968).

Laboratory Techniques in Biochemistry and Molecular Biology. Vol. 1. By *T. S. Work* and *E. Work*, North-Holland Publishing Comp., Amsterdam 1970. 1st ed., 572 pp., numerous figs. and tab., bound, DM 90.—.

The current rapid progress in natural sciences is largely due to the development of new methods of analysis and separation which give high sensitivity and resolution. However, these methods are often so difficult to perform and interpret that they can only be mastered and usefully employed by an expert. Nevertheless, they can be learned directly or indirectly from someone experienced in their use.

The North-Holland Publishing Co. were alert to this need and have started a series on "Laboratory Techniques in Biochemistry and Molecular Biology" under the general guidance of *T. S.* and *E. Work*. The aim of this series is to give practical instruction and information on the use of modern methods. The initial contributions are on gel chromatography (*L. Fischer*, Uppsala), gel electrophoresis (*A. H. Gordon*, Mill Hill) and immunochemical reactions (*J. Clausen*, Copenhagen), bound together into one sturdy and attractively presented volume. In each case there are detailed notes on the use of the method, the way in which the instruments used work, and on critical evaluation of the results: there is also a list of suppliers and commercially available variants.

The individual sections live up to the promise of their authors' reputations, even on close and critical study.

Rapid developments in this field will of course mean that now there are even more recent variants of instruments, which no longer have the faults of their predecessors, and this inevitably overtakes a carefully compiled book such as this. Examples of omissions due to this factor include a detailed account of the electrofocusing technique, rapid analysis of enzymes in acrylamide gel, the more recent gel electrophoresis methods, the theoretical derivations for particle weight determination of proteins by gel filtration, and many others. But the material that is here is first class and extremely useful for any practising biochemist. The individual sections of the hard cover compilation are to be issued as separate paperbacks, which is very sensible, since any experimenter who is using or thinking of using these methods will want the appropriate book at hand. It would also be a good idea if these were just as sturdily bound as the main volume, since it is probable that they will be handed around from one worker to the next.

L. Jaenicke [NB 982a IE]

Laboratory Techniques in Biochemistry and Molecular Biology. Vol. 2. By *T. S. Work* and *E. Work*, North-Holland Publishing Comp., Amsterdam 1970. 1st ed., 408 pp., bound, Dfl. 75.—.

The second volume of "Laboratory Techniques" consists of two very timely sections: automatic enzyme determination, and the principles of cellulose-exchanger chromatography.

D. B. Roodyn, known as the author and editor of a whole series of extremely valuable monographs, here presents a review of over 200 pages of the techniques by which serial analysis and series of analyses needed in modern clinical and biochemical laboratories can be automated and programmed. Although as far as equipment is concerned the author places most emphasis on the Technicon Autoanalyzer, his presentation is by no means one-sided, since he tries to bring out the fundamental principles and to be just to the other methods. This is extremely well done. Descriptions are given of continuous and discontinuous sampling, single and multiple enzyme analyses, serial characterization of the physicochemical parameters of enzymes, data processing, and presentation of the results. In an appendix a FORTRAN program for a general enzyme analysis system is given, together with a summary of all the published automated enzyme determinations up to 1968. For all his enthusiasm for his subject, the author's presentation is critical and balanced. This is a book by a practical man for the practical man, who will here find an advisor reliable in every respect.

Before any chemical research can begin, the substances to be used or investigated must be purified. For complex biological materials and macromolecules, ion exchangers based on cellulose have very recently been introduced and have proved themselves extremely useful. *E. A. Peterson* is one of the pioneers in this field. His 170-page monograph results from the wealth of experience he has accumulated over the past 15 years. It begins with a description of the cellulose ion exchanger, and then turns to the theoretical foundations of chromatography and the effect of varying the parameters. The next sections, of special value from the practical viewpoint, deal with selection of the chromatographic conditions, preparation of the exchanger, packing and charging of the columns, the actual way in which elution is carried out, and treatment of the eluate. Finally, some current biochemical applications of importance are described. Here too valuable tips are given and the commercially available instruments are listed. The wealth of information given will enable even the novice chromatographer to approach his task with a certain amount of confidence and to make sense of his findings.

In both parts of this book the clear presentation, the circumspect and practical arrangement of the material, and the excellent appearance are particularly praiseworthy. This book should be available to every biochemist.

L. Jaenicke [NB 982b IE]

Gas Chromatography, Principles, Techniques and Applications. By *A.B. Littlewood.* Academic Press, New York 1970. 2nd. Edit., 546 pp., 152 figures, DM *ca.* 90.—.

The second edition of *Littlewood*'s book, like the first, is divided into three general sections on principles, techniques, and applications of gas chromatography. The strength of the book lies in the particularly clear and lucid treatment of the theory in Chapters 1–6. However, the discussion of the theoretical relations separately from the applications in the last few chapters will occasionally make it difficult for the analyst using the book to find explanations for practical observations that he is unable to interpret. Moreover, a comprehensive treatment of the diverse applications of gas-chromatographic methods can scarcely be achieved in the space of one textbook. Applications should be discussed in a textbook only to make the relations easier to understand and to facilitate the use of the special literature. This task is approximately fulfilled by the last part of the book.

As far as the second part of the book is concerned, the reviewer is of the opinion that it would have been better to place the emphasis on other phenomena and relations. The theory and construction of detectors such as the thermal conductivity cell and the argon detectors are described in too much detail. The analyst nowadays *buys* an instrument or an important part of an instrument, such as a detector, and will only rarely be able to make technical modifications and improvements. The properties of a detector that play a large part in determining the reliability and accuracy of quantitative analyses, such as sensitivity, dead volume, linear dynamic range, drift behavior, and calibration factors are important in this connection. The treatment of the argon detectors, with the possible exception of the electron capture detector, in no way reflects their practical importance, which is decreasing. Chapters 9 and 10 could have been shortened in favor of Chapter 11 in particular. Reaction gas-chromatographic methods and combined methods, column changing techniques, and automation of the analysis and of the evaluation are more important than some relations discussed in Chapters 9 and 10.

Finally, the reviewer would ask the publisher to make the print clearer and to draw more attention to important conclusions and basic principles by the use of bold type and indentations. To sum up, we can only say that the strength of the book lies in the clear and easily understandable treatment of the theory, though the book can also provide some important hints for practical problems.

Gerhard Schomburg [NB 973 IE]

Physical Chemistry, an Advanced Treatise. Vol. IV: Molecular Properties. Edited by *H. Eyring, D. Henderson,* and *W. Jost.* Academic Press, New York–London 1970, 1st Edit., xx, 832 pp., numerous figures, $ 39.—.

All the important fields of physical chemistry are to be covered in eleven volumes by well-known specialists for scientists and advanced students. Three volumes deal with properties of atoms and molecules: III. Electronic Structure of Atoms and Molecules, IV. Molecular Properties, and V. Valency. The present volume IV contains the following chapters: 1. The Variety of Structures Which Interest Chemists *(S. H. Bauer)*; 2. Rotation of Molecules *(C. C. Costain)*; 3. The Vibrations of Molecules *(G. W. King)*; 4. Vibrational Spectra of Molecules *(J. R. Hall)*; 5. Spectra of Radicals *(D. E. Milligan* and *M. E. Jacox)*; 6. The Molecular Force Field *(T. Shimanouchi)*; 7. Interactions among Electronic, Vibrational, and Rational Motions *(J. T. Hougen)*; 8. Electric Moments of Molecules *(A.D. Buckingham)*; 9. Nuclear Magnetic Resonance Spectroscopy *(R. M. Golding)*; 10. ESR Spectra *(H.G. Hecht)*; 11. Nuclear Quadrupole Resonance Spectroscopy *(E. Schempp* and *P.J. Bray)*. 12. Mössbauer Spectroscopy *(N.N. Greenwood)*; 13. Molecular-Beam Spectroscopy *(C.R. Mueller)*; 14. Diffraction of Electrons by Gases *(S.H. Bauer)*.

Many chemists successfully apply physical methods to the determination of molecular properties. However, their theoretical knowledge is at best superficial, since many detailed discussions are incomprehensible to them and seem difficult to apply on the basis of their earlier training. This series is therefore very welcome in its aim of guiding the chemist to a high level in the fields of physical chemistry. Most of the authors do in fact manage to make the theory accessible, in as much detail as is necessary, by means of useful formulas and examples. Experimental data are kept very brief, while the range of applications is outlined with typical examples, numerous tables, and comprehensive literature lists. The book is excellent and stimulating, and I hope that it will be widely used, with many advanced students among its readers.

Bernhard Schrader [NB 974 IE]

Phase Diagrams, Materials Science and Technology. Vol. II. The Use of Phase Diagrams in Metal, Refractory, Ceramic and Cement Technology. By *A. M. Alper.* Academic Press, New York–London 1970, 1st Edit., viii, 354 pp., numerous figures, bound $ 16.—.

Whereas Volume I[1] was concerned mainly with the thermodynamic principles and the theoretical aspects, the emphasis in Volume II is entirely on practical applications. It begins with a short section by *A. Muan* on the influence of the oxygen partial pressure on the formation of oxides of the types A_2O, AO, *etc.* This section is made easy to understand by the fact that general diagrams for the binary, ternary, *etc.* cases are given first and are then discussed further for particular systems such as wüstite-magnetite *etc.* The equations in this section are not entirely free from errors, but this should not trouble the user too much.

This section is followed by nine monographs. The relation between the phase equilibrium and the constitution and fine structure in ceramic-metal systems *(J. White)* and the use of these systems in cement chemistry *(F. P. Glasser; D. L. Johnson,* and *I. B. Cutler)*, in the industrial bonding of different metals or of metals and ceramic materials *(A. Prince)*, and for the production of refractory materials *(H. M. Kraner* and *A. M. Alper; R. C. Doman, R. N. McNally,* and *H. C. Yeh)* are discussed. Heat treatment for the production of alloys having given properties *(G. Krauss* and *J. F. Libsch)* and its relation to phase equilibria in multicomponent systems are discussed here, as is the application to extraction metallurgy *(J. Taylor)*. Special mention should be made of a detailed thermodynamic and molecular-theoretical article by *T. B. Massalski* and *H. Pops* on the stability and classification of intermetallic phases, which satisfactorily shows the significance of the atomic structure in the consideration of the diagrams.

Like the first volume, the present second volume can be warmly recommended to all those involved in scientific and practical studies in the field in question.

Klaus Schäfer [NB 970a IE]

Phase Diagrams, Materials Science and Technology. Vol. III. The Use of Phase Diagrams in Electronic Materials and Glass Technology. By *A. M. Alper.* Academic Press, New York–London 1970. 1st Edit., xviii, 325 pp, numerous figures, bound $ 16.50.

This third volume deals mainly with applications of phase diagrams to the production of substances having predetermined properties. The substances in question are mainly semiconductors, but nonconductors such as glass are also discussed.

The volume begins with a fairly long article on crystal growth *(J. W. Nielsen* and *R. R. Monchamp)*. The techniques for the production of very pure semiconductor materials are briefly described, and the aptness of one method or another is discussed on the basis of the phase diagram, e.g. the production of single crystals in the neighborhood of and at a "greater" distance from a stoichiometric composition. Closely related to this are applications to the synthesis of semiconductor materials consisting of two or more components *(M. B. Panish)*.

A short article *(V. F. Zackay, M. F. Merriam,* and *K. M. Ralls)* is devoted to the recently used superconduction in rapidly cooled systems for the characterization of new crystalline states in alloys; the superconduction is also discussed in the more general section on rapidly cooled metastable alloy phases *(B. C. Giessen* and *R. H. Willens)*.

The last four chapters deal with the miscibility gaps in liquid metal oxides *(E. M. Levin)*, the relations between phase diagrams and the structure of glass-forming oxide melts *(E. F. Riebling)*, cryoscopy in salt melts *(T. R. Kozlowski)*, and the kinetics of the dissolution of solid phases in solvents *(A. R. Cooper)*. In this last section, the phase diagrams are used as an excellent source of the data that characterize a solution; they may thus be regarded as a means of predicting the final solution behavior. The section, though only short, gains special importance through the contributions on glass formation and cryoscopy.

This volume, which is entirely written by leading scientists closely connected with industry, is almost more important than the previous two to industrial engineers or chemists.

Klaus Schäfer [NB 970b IE]

[1] Cf. Angew. Chem. internat. Edit. *10*, 205 (1971).

Aquatic Chemistry. By *W. Stumm* and *J. Morgan*. John Wiley and Sons Ltd., Chichester 1970. 1st ed., 583 pp., bound, £ 11.75.

This is an excellent textbook. In collaboration with *Morgan*, *Stumm* has developed his Harvard lectures into a compendium in which the fundamental chemical reactions in aquatic chemistry are described, with particular emphasis on the thermodynamic aspects. The clear layout of the sets of formulas and the illustrative matter is a considerable aid to the student. The authors' aim to establish a theoretical basis for the chemical behavior of natural waters, *i.e.* the oceans, estuaries, rivers, lakes, and ground water, has been quite definitely achieved.

The consideration of the chemical processes involved in the distribution and circulation of chemical substances in natural waters, the fundamental reactions taking place during water treatment, and the quantitative mathematical treatment of the variables which determine the composition of natural waters, are all amplified by numerous exercises and calculations drawn from practical experience. It is precisely this that gives the work its vigor as a textbook, and will remind even the already qualified worker that it is worth while having another look at thermodynamics.

Wilhelm Husmann [NB 979 IE]

The Neurosciences: Second Study Program. Ed. by *F.O. Schmitt*. The Rockefeller University Press, New York. 1st Edit., 1970, 1100 pp. 607 figures. Linen, $ 30.— for individuals, $ 60.— for libraries.

"We are at the beginning, and not near the end, of the process of understanding development. This is not the time to summarize, but a time to prospect and project into the future; and the best thing is to turn for guidance to the living object which teaches us the lessons and also teaches us the real problems to which we are to direct our questions". This quotation from *Paul Weiss*, reproduced at the beginning of one of the chapters, could well serve as a motto for the book as a whole. It is of course true that this is already the second report of a three-week conference of the Neurosciences Research Program, the first having been published in 1967. It is also true that the report's 1000 or more pages of A 4 size offer the reader an outstanding survey of current knowledge of the structure and function of animal and human nervous systems. Nevertheless, it is precisely from these facts that it follows just how incomplete and in many respects rudimentary this knowledge is. There are many reasons for this situation: The extraordinary complexity of the brain, which is never likely to be completely unraveled with the methods presently available, the inability to carry out experimental work with the human brain—although it is precisely this organ which has undergone the greatest change in the course of man's evolution from his animal forebears, and which must therefore show much weaker analogies to the corresponding animal organ than in the case of, say, the liver, lungs, or the kidney—and finally the problem that the integrating functions of the brain (learning, memorizing, thinking, feeling) are at best difficult, if not impossible to quantify. And yet, one must not lose sight of the fact that, like all other organs in the human body, the brain involves physical and chemical processes, and that what we call intellect stems from a finely balanced interplay of molecules and ions. Anyone who approaches this volume from this standpoint and who is not deterred by the profusion of anatomical and biological terms perhaps unfamiliar to the chemist, will find himself richly rewarded. Eighty-eight chapters cover eight general subjects:

Evolution of brain and behavior
Development of the nervous system
Determinants of neural and behavioral plasticity
Complex psychological functions
Neural subsystems and physiological operations
Communication and coding in the nervous system
Aspects of molecular neurobiology
Recognition and control at the molecular level

The volume is copiously and instructively illustrated. Unfortunately, in the case of figures taken from other books, abbreviations are sometimes reproduced without explanation. Whereas this may be all right for the initiated, it does represent an additional difficulty to those less familiar with the field. It is to be hoped that the editors of future volumes of this kind will generally have a thought for interested scientists working in adjacent disciplines, on whose collaboration neuroscience research will after all have to rely if it is to make any real progress. More diagrams, to explain the principles involved or the terminology used, would be of tremendous help, even when they might be familiar to the specialist. Notwithstanding such reservations, the present volume, like its predecessor, undeniably represents a historic milestone in the literature on neurosciences research.

Helmut Grünewald [NB 971 IE]

Arzneimittelwirkungen (Effects of Pharmaceuticals). By *E. Mutschler*. Wissenschaftliche Verlagsanstalt, Stuttgart 1970. 1st ed., xvi, 477 pp., 77 figs., bound, DM 48.—.

The object of this book was to provide an introduction to pharmacology for pharmaceutical chemists, chemists, and biologists, at the same time giving them the requisite background knowledge of medicine. Accordingly, the book contains introductory chapters on anatomy and physiology, which present what is needed for understanding of this subject in brief, precise, and memorable form. This is helped by the chapter "Explanation of medical terms" at the end of the book, and also by the extensive and extremely useful subject index.

In the general part of the book the author explains important pharmacological concepts such as conditions of action, receptor theory, structure-effect relationships, and side effects. In the following, more specific, section he deals with the nervous system, endocrine glands and their hormones, circulation, kidneys and the urinary tract, the gastrointestinal tract, essential substances, infective diseases, chemotherapy of malignant tumors, and poisoning.

The author knows how to clarify and impress on the reader the difficult interrelationships of this complex subject. He has also undertaken to keep his book continually updated, which in view of the rapid development of this field will be quite a task. This can be seen from the fact that today, only a year after the appearance of the first edition, there is already additional material to be added (*e.g.* the inclusion of L-Dopa therapy in the section on Parkinson's desease).

With this book, *Mutschler* has undoubtedly fulfilled his aim of providing instruction in pharmacology together with the appropriate background knowledge of medicine. Every scientist concerned with pharmacology should have a copy. It should also prove to be a useful source of information for doctors.

Ernst Biekert [NB 980 IE]

Molecules and Life. An Introduction to Molecular Biology. By *M. V. Volkenstein*. Plenum Press, New York—London 1970. 1st ed., xii, 513, pp., 207 figs., numerous tab., bound, $ 15.00.

Physicists who had become tired of their subject may boast of having opened the field of molecular biology. Provided that they are not regarded merely as molecular geneticists, they can be said to have used the tools and the underlying philosophy of physics to place biology on a quantitative footing. Since then any physicist writing on a topic such as molecules and life has always aroused great expectations. In the present case, however, these expectations have not been fulfilled; this is not a work of startling originality, but rather a mediocre presentation of biochemistry from the viewpoint of a physicist, *i.e.* without any chemistry. The fundamentals of physical chemistry and information theory are painstakingly laid out, and an attempt is made to use them to describe biological processes mathematically. This is certainly valid, very important, and it has never been correlated in a book in this way before. But whom is it going to help? The many biological platitudes will be of no use to the physicist, though they may well bring a smile to the face of the biologist; he in his turn will not understand the physical topics in the manner in which they are presented. The book is thus a failure, although it must be admitted that all the physical problems are derived in a completely unambigous manner. They remain, however, just as dull as the entire surrounding structure, which has been diligently but unimaginatively stuffed full of facts. There is a great need for a textbook of biophysical chemistry or physical biochemistry, or whatever one may choose to call it, but this book will not make any student enthusiatic over molecular biophysics.

Some absurdities in the text are not the fault of the translation, which could not get far enough away from the original, as a comparison with the German edition will show. In both cases one is assured that the manuscript has been specially revised for that particular language version. Personally, I was unable to find any differences, and in some cases even the same slips occur (*e.g.* "lamp filament chromosome").

A truly stimulating textbook on molecular physics still remains to be written. When it appears, let us hope that the author is not so much of a self-made biologist, and also has a fresher style of writing.

L. Jaenicke [NB 981 IE]

Art in Organic Synthesis. By *N. Anand, J. Bindra* and *S. Ranganathan*. Holden-Day, Inc., San Francisco 1970. 1st ed., xiv, 414 pp., numerous figs., bound, $ 11.00.

"There is excitement, adventure, and challenge, and there can be great art, in organic synthesis". With these words of *R. B. Woodward*, one of the great pioneers in organic synthesis, as a motto, the authors have collected together in alphabetical order more than 100 examples of post-1940 syntheses which are characterized by their intelligent planning and their use of novel reactions and reagents. The compounds synthesized are natural products or unusual or strained molecules which were prepared in order to confirm their predicted properties. A few examples will give an idea of the high standard of selection: aflatoxin B_1, aromatic $(C_nO_n)^{2-}$ ions (squaric acid, *etc.*), normal and bridged annulenes, bullvalene, chlorophyll, colchicine, Dewar benzene, α-ecdysone, helicin, morphine, penicillin, quinine, twistane, and vitamin B_{12}. Each synthesis is presented clearly and concisely, with a short introduction of principles and special features, a clearly presented reaction scheme, and literature references. The indexes at the end of the book are arranged by names of reactions, types of reaction, reagents, authors, and substances. The literature has been reviewed up to the middle of 1969. There are a few printing errors and some unhelpful abbreviations, but these hardly detract from the usefulness of the book.

This work is more than a collection of examples for seminars and lectures on organic synthesis. It offers the practising chemist an invaluable guide to the selection of analogous reactions, methods and reagents and also serves as a literature source. Particular attention is paid to the strategies (so important in the solution of complex synthesis problems) for the selection of key and relay compounds, converging synthetic routes, *etc.* Since the selection of syntheses is representative, there is also the possibility of using the frequency of references in the reaction name index as a highly informative indication of the range of possibilities of a given method in research and teaching. The book can be recommended as a valuable information source for all branches of organic chemistry.

Burchard Franck [NB 983 IE]

Molten Salts. Characterization and Analysis. Ed. by *G. Mamantov*. Marcel Dekker, New York 1969. 1st ed., xvi, 611 pp., bound, $ 16.75.

This book contains twenty papers from a symposium held at Atlantic City in September 1968. The first three contributions deal with the fundamental ideas of structure and energetics of molten salts, the concept of complex ions in ionic melts, and relationships with phase equilibria. The next six papers concern the results of ultraviolet, infrared, and Raman spectroscopy, NMR spectroscopy of ^{205}Tl salt solutions, and the use of neutron diffraction in the study of short-range order. In the four papers devoted to transport, the introduction of the glass-transition temperature for the treatment of low-melting systems is noteworthy, as also are the proof of electron conduction, *e.g.* in Cu^{I}/Cu^{II} halide solutions, and the use of ultrasonic relaxation. The other papers are on miscellaneous topics, including distribution equilibria between metal and fluoride melts, double-layer capacity at dropping electrodes, solubility of halogens, electrode reactions in fluoride melts, chronopotentiometric studies, and lastly the thermochemistry and mechanism of redox reactions of oxygen in nitrate melts.

All the contributions include recent research results relating to a more or less limited part of the entire field; however, most of them take the form of comprehensive reviews, and from the subject viewpoint they are brought together in such manner that even the reader new to the subject will obtain a full and up-to-date picture.

There is also a great deal of detailed information on experimental techniques and material problems. The book is thus of interest not only to those immediately concerned with the chemistry of molten salts, but also to anyone concerned with chemical processes at high temperatures.

Hubert Kühnl [NB 984 IE]

Introduction to Electronic Absorption Spectroscopy in Organic Chemistry. By *E. S. Stern* and *C. J. Timmons*. Edward Arnold Publ. Ltd., London 1970. 3rd ed., vi, 277 pp., numerous figs., bound, £ 5.10.

The present book, the extensively revised 3rd edition of Gillam and Stern, deals with electron absorption spectroscopy in organic chemistry. In less than 300 pages the authors have only two possibilities: either a presentation of the basic theory with brief illustrative examples of spectra or an interpretation of the results with appropriately chosen theoretical data. They have in fact chosen the latter course.

The book is clearly arranged and is divided into ten chapters. In Chapter 1 the general basis of spectroscopy is discussed, and this is followed by the measurement and representation of absorption spectra. It should be particularly noted that the authors emphasize the physically meaningful presentation of spectra by means of wave numbers (p. 23). Chapter 3 gives a general survey of the basic principles and examples of the assignment of spectral bands on the basis of a large amount of experimental material. Chapters 4—7 review the spectra of the more important chromophore systems: molecules with only one functional group, conjugated chromophore systems, aromatic hydrocarbons with derivatives, and hetero-aromatics. The value of this chapter is enhanced by the numerous graphical presentations, spectra, and tables. Chapter 8 deals with the application of absorption spectroscopy to qualitative analysis, Chapter 9 with the spectroscopic determination of organic compounds, and the last chapter with the relationships between UV absorption spectroscopy and molecular structure.

The appendix reviews the bibliography of electron spectroscopy and also gives general information on solvent and temperature effects. A detailed list of references is appended to each chapter. The book is clearly printed and is easy to read.

It is thus a valuable and needed complement to the many works on electron excitation spectroscopy with their predominantly theoretical basis, and can be recommended to any student of chemistry.

H. H. Perkampus [NB 987 IE]

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Imaging and Analysis of Surfaces with a Scanning Electron Microscope and Electron Spectrometer[**]

By Reimer Holm[*]

The topography and the composition of a surface are in many cases of equal importance (catalysis, electroplating, pretreatment of foils and sheet metal, corrosion, passivation, adsorption, coating of fibers, etc.), and this explains the great interest in methods of investigation that reveal both. If the demands on the resolving power, the analytical possibilities, and the thickness of the surface layer are not too exacting, combined devices like the scanning electron microscope and its analytical accessories can be used. When it is necessary to avoid the compromises involved in simultaneous imaging and analysis, the investigations must be carried out with separate equipment. As an example of a method for the analysis of surfaces we consider briefly photo- and Auger electron spectroscopy (ESCA).

1. Principle of the Scanning Electron Microscope

It has been an old dream of scientists to possess a device enabling them to image a surface with the highest possible spatial resolution, *i.e.* to study its topography, and in addition to obtain the most complete possible information on the composition of this surface. There is, at present, no such universal apparatus, although numerous attempts have been made using electrons, ions, and X-rays[1]. The scanning electron microscope may be considered as a good approximation as regards the demands of microscopy. As a supplement to this we shall discuss a special surface analysis technique which utilizes photo- and Auger electron spectroscopy with X-ray excitation (ESCA). The two methods have, in comparison with others, the advantage that preparation is fairly easy, that they can be used universally, and that they are therefore suitable for routine industrial investigations.

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[**] Since it is impossible to list the large number of publications dealing with the scanning electron microscope; the reader is referred to the following bibliographies:

O. C. Wells; IBM Research Center
Post Office Box 218
Yorktown Heights
New York 10598 (USA)

G. Pfefferkorn and *U. Ehrenwerth*; Institut für medizinische Physik der Universität
44 Münster, Hüfferstrasse 68 (Germany)

The idea of a scanning electron microscope goes back to *M. Knoll* and *M. von Ardenne*. It was taken up again by *Oatley et al.*[2a] and applied to the imaging of the surfaces.

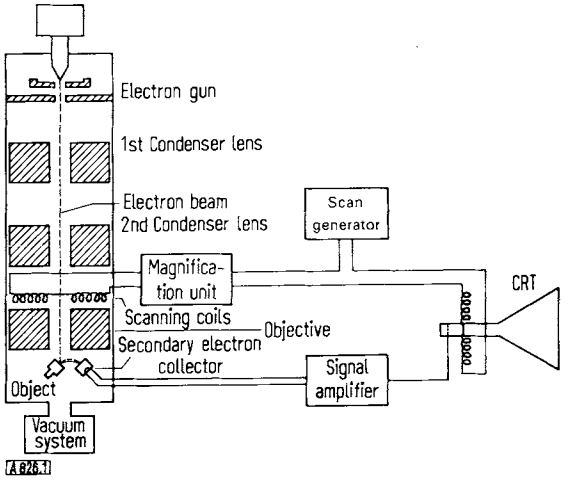


Fig. 1. Block circuit diagram of a scanning electron microscope ("Stereoscan", Cambridge Scientific Instruments).

The scanning electron microscope works on the pantograph principle: The essential elements are two electron beams operated synchronously by a scan generator (Figs. 1 and 2). The primary beam is produced in an evacuated column by thermionic emission, and is focused to a dia-

meter of about 100 Å by electromagnetic lenses. This beam scans the object point by point and line by line. The other beam records the picture point by point and line by line

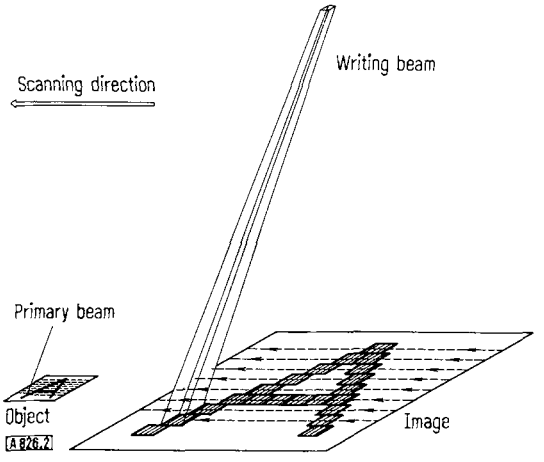


Fig. 2. Analysis and reconstruction of a picture by the scanning method (according to [2b]).

on the phosphor screen of a cathode ray tube. The magnification is given by the ratio of the picture area to the scanned area of the object.

When the primary beam impinges upon the object, a variety of interactions occurs between the electrons and the solid material (Fig. 3). Both secondary electrons and

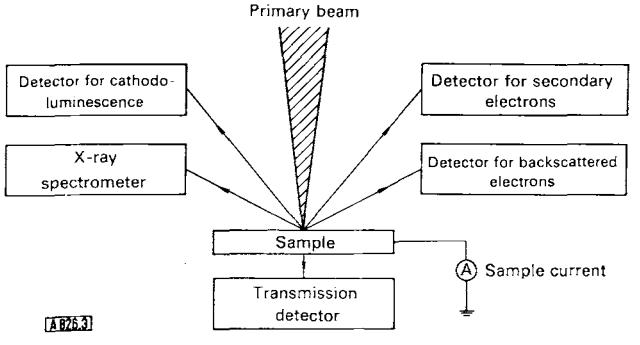


Fig. 3. Interactions between electrons and matter inserted in the scanning electron microscope for picture formation.

backscattered electrons are used for imaging the surface. The secondary electrons are generated by impact ionization or the Auger effect. They possess a significantly lower energy than the primary electrons and those that are backscattered elastically or with only small energy losses. The secondary electrons are collected by a side-mounted positively charged electrode and are processed in the attached electronics so that their number controls the brightness of the corresponding point on the CRT screen. In such an imaging device there is no limitation by a particular lens optics. In particular, the aperture of the primary beam is very small (10^{-2} to 10^{-3} rad $\approx$ 0.6 to 0.06°). One thus obtains a depth of field that is at least 500 times greater than that of the optical microscope.

The number of secondary electrons emitted depends on the properties of the region struck by the beam (Fig. 4)[3a]. The incident primary electrons penetrate the surface of the sample, and in the schematically drop-shaped region drawn secondary electrons are released by scattering processes. Only a few of them have a chance of leaving the surface. On spikes and edges the escape surface becomes much larger than for a smooth plane surface, and the spikes therefore appear bright (relief contrast). Heavy elements emit better than light elements (material contrast), and an electric field may inhibit or enhance the yield coefficient (potential contrast).

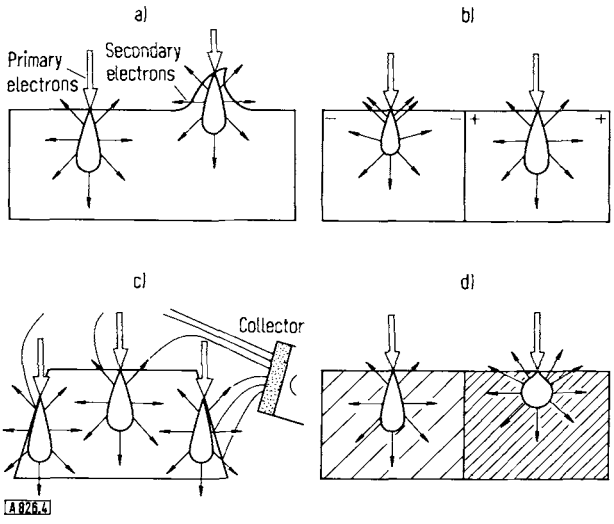


Fig. 4. Contrast mechanisms in secondary electron pictures in the scanning electron microscope (according to [3b]).

(a) Effect of topography: spikes and edges are brighter than plane surfaces.

(b) Effect of electric charge: negatively charged points are brighter than positively charged ones.

(c) Effect of position relative to the collector: a surface turned toward the collector is brighter than one turned away from it.

(d) Effect of chemical composition: regions of heavy elements are brighter than those of light ones.

The secondary electrons are never emitted only from the point of incidence of the primary beam, but always come from a certain diffusion region around it. This diffusion region is particularly small in heavy metals, and thus in this case it is possible to obtain a spatial resolution of about 200 Å; this corresponds to a useful magnification of 5000 to 10000 times.

Conducting objects can be investigated in the scanning electron microscope without any particular preparation. To avoid electrostatic charging, insulating samples must be coated with conducting substances. Carbon is chosen as a high-adhesion conductive coating, and to improve the resolving power and secondary electron emission yield, roughly 200-Å thick coating of gold is evaporated on top of this.

2. Applications of the Scanning Electron Microscope

The illustrated examples, which are taken mainly from the fields of process engineering and applications technology, cover only a small part of the many possibilities of the scanning electron microscope. The nonwoven fabric used as a dust filter (Fig. 5) and the knotted wool fiber

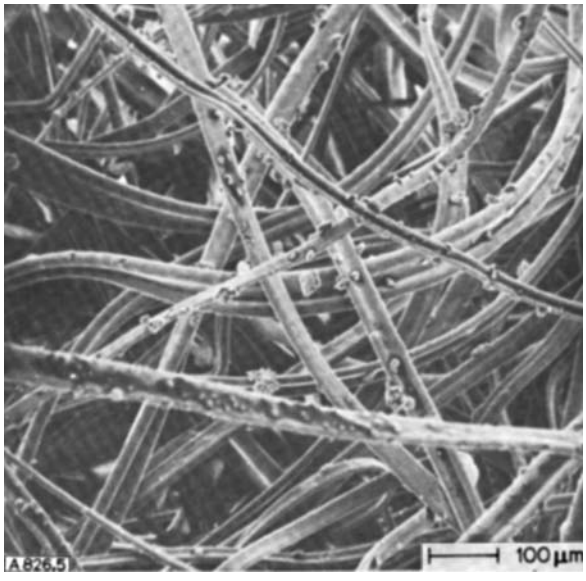


Fig. 5. Nonwoven fabric used as a dust filter.

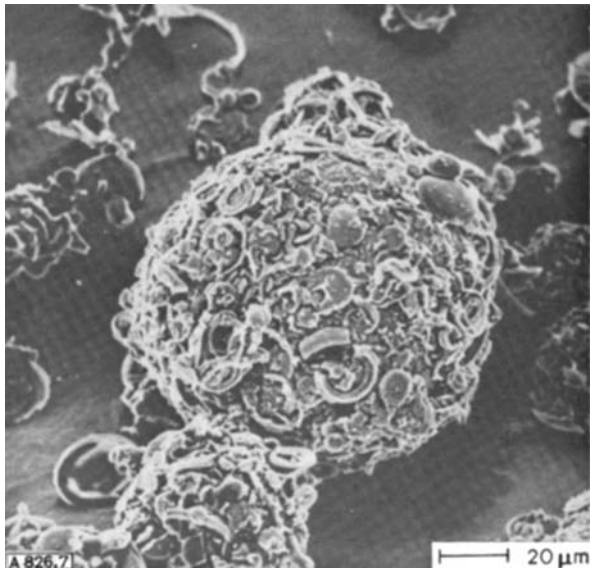


Fig. 7. Latex rendered flowable by diatomaceous earth.

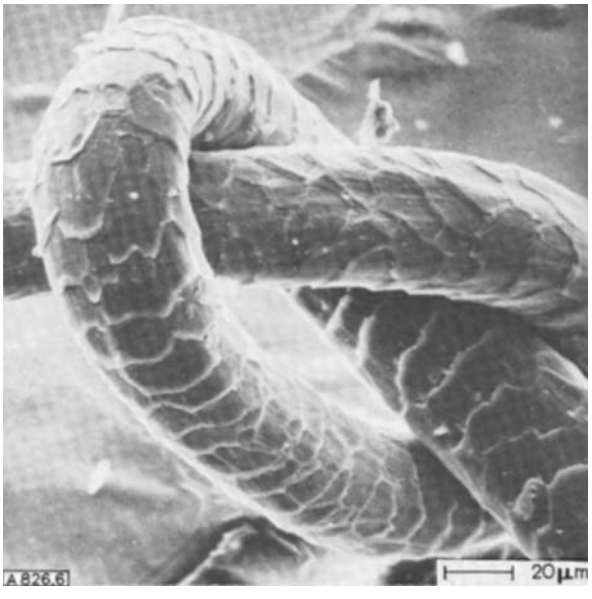


Fig. 6. Knotted wool fiber.



Fig. 8. Corroded steel surface.

(Fig. 6) demonstrate the depth of field of the microscope. In the case of the polybutadiene latex in Fig. 7 it is easy to see the diatoms which were used to make it flowable. Fig. 8 shows a nonuniformly corroded metal surface, with remains of nonconducting corrosion products visible in the depressions. In contrast to the light-optical picture they appear bright, as a result of charging.

Figures 9—12 show several stages in leather processing[4]. The grain layer (Fig. 9) is roughened (Fig. 10), then impregnated (Fig. 11) and primed (Fig. 12). The lacquer can now be applied. This should be compared with the surface of a microporous foil (without finish), used as a synthetic leather, Fig. 13. Carbon crystals with the theoretically required helical structure are often found in pyrolysis furnaces[5]. The twinned crystal shown in Fig. 14 was produced by the coalescence of two closely neighboring cylindrical crystals, both of which had originally their own helical structure.

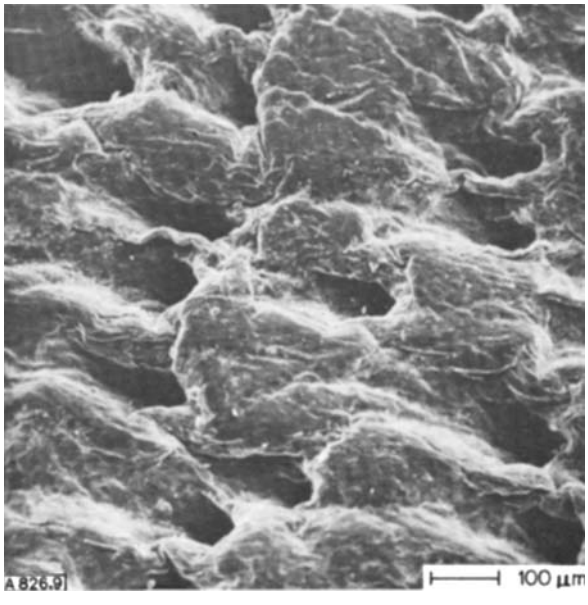


Fig. 9. Grained layer of leather.

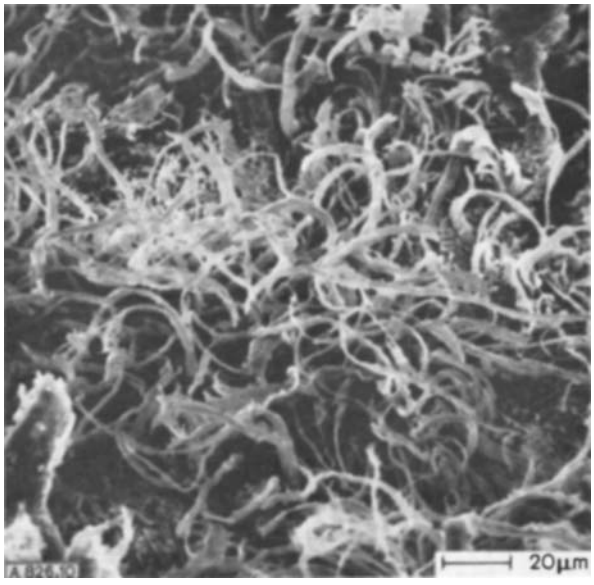


Fig. 10. Grained layer of leather, roughened.

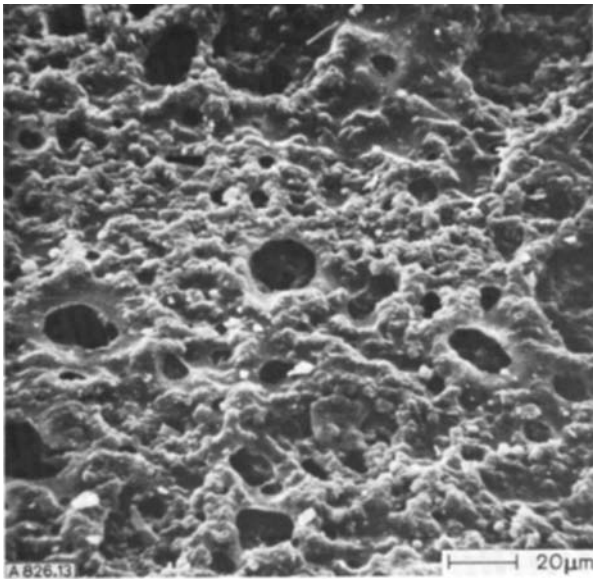


Fig. 13. Unfinished surface of a microporous foil.

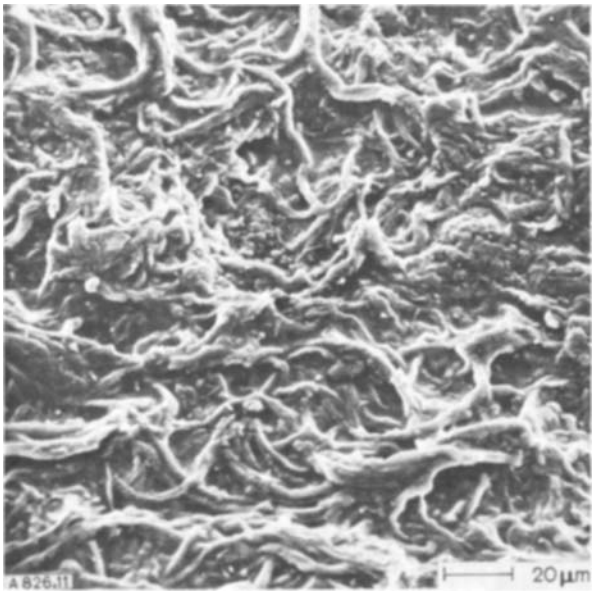


Fig. 11. Grained layer of leather, roughened and impregnated.



Fig. 14. Carbon crystal from a pyrolysis furnace.

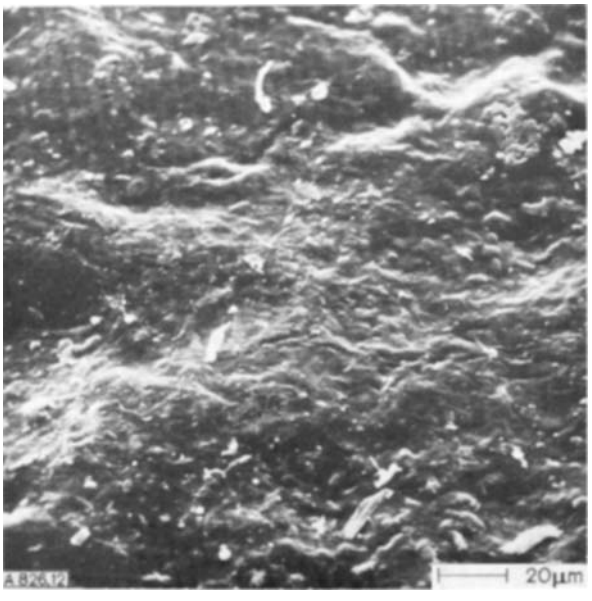


Fig. 12. Grained layer of leather roughened, impregnated, and primed.

Because of the depth of field it is very easy to photograph fracture surfaces, *e. g.* of high polymers, with the aid of the scanning electron microscope. Interpretation of the pictures in order to get a relationship between the morphology of the fracture surface and the macroscopic deformation processes for high polymers is still only tentative. One has to consider the physical (*e. g.* the free volume) and the chemical structure of the material (*e. g.* in the case of ABS the styrene-acrylonitrile copolymer matrix with discontinuously distributed polybutadiene), as well as features that are connected with the fracture process itself (*e. g.* deformation rate).

Figures 15 and 16 give a clear example of this case: the ABS polymer, the deformation rate, and the fracture temperature are the same in both cases. Figure 16 shows a structure typical for a fracture with large plastic deformation (crazing) while Fig. 15 resembles brittle fracture, perhaps a low-temperature fracture. The difference lies in the physical structure: the specimen of Fig. 16 is freshly

extruded, while that of Fig. 15 has been stored for a long time at room temperature or somewhat above it. The example shows that investigations of fracture surfaces of polymers are only meaningful if the thermal and mechanical history of the specimens is taken sufficiently into account[6].

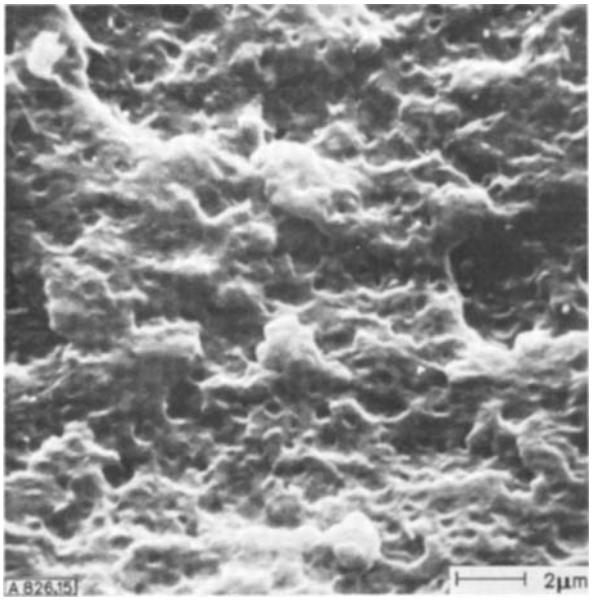


Fig. 15. Fracture surface of an ABS polymer after prolonged storage.

The properties of polymers reinforced with glass fibers depend to a large extent on the adhesion between the matrix and the glass fibers; the adhesion is improved by the addition of special coupling agents[7]. Figure 17 is typical of poor adhesion: long unwetted glass fibers stick out of the fracture surface. Fig. 18 shows, on the other hand, a relatively good adhesion: the fracture runs predominantly in the matrix, the fibers are wetted. Mechanical measurements can detect smaller differences than the scanning electron microscope, but they are not so easy to interpret.

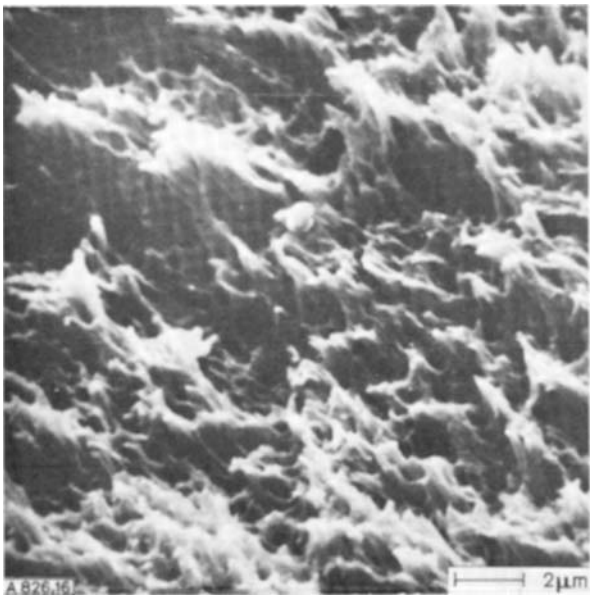


Fig. 16. Fracture surface of a freshly extruded ABS polymer.

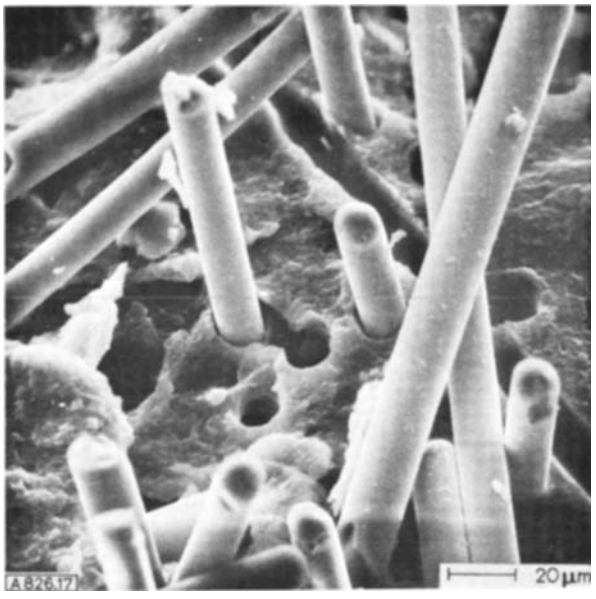


Fig. 17. Fracture surface of a glass-fiber-reinforced polymer with poor adhesion between the matrix and the glass fiber.

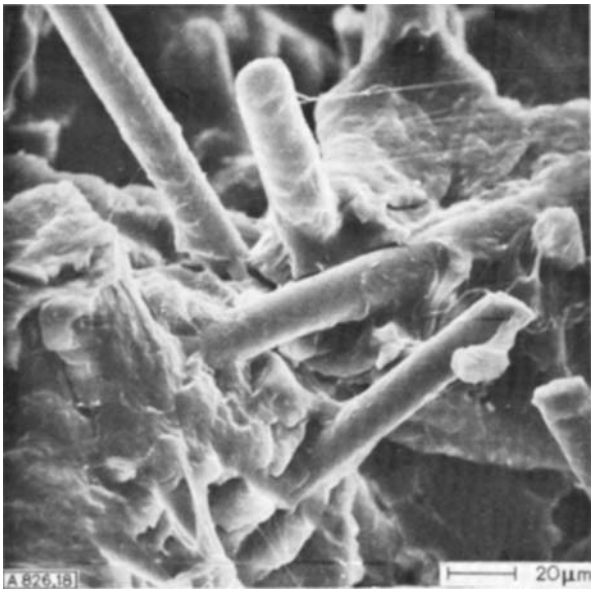


Fig. 18. Fracture surface of a glass-fiber-reinforced polymer with good adhesion between the matrix and the glass fiber.

With a suitable arrangement of the primary beam, the sample, and the collector, the scanning electron microscope already gives striking three-dimensional pictures. The impression of depth can be increased further by taking proper stereoscopic pairs[8]. Unfortunately, for various reasons the measurement of height, as in photogrammetry, is subject to large errors.

The pictures illustrating this paper were taken with a scanning time of 40—100 s. The development of new scanning coils has made it possible to scan at television frequencies, though with a certain loss of picture quality. Thus one can observe dynamic events like the stretching of foils and fibers with the scanning electron microscope[9].

In all the cases considered so far the scanning electron microscope has been used as a pure microscope. Because of its depth of field, it is applied above all to the imaging of

rough fracture and outer surfaces. There is an increasing interest in going beyond mere imaging to examine the composition of the surface. Material differences of the surface may be detected with the scanning electron microscope either chemically by selective etching and staining[10] or physically by exploiting the different interactions between the electrons and the solid. As an example of the first class, one might consider etching with oxygen in a gas discharge (cold combustion), *e.g.* to separate inorganic

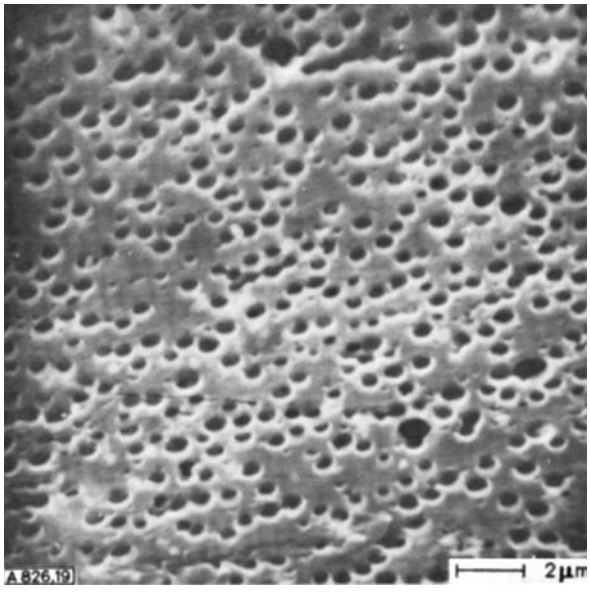


Fig. 19. ABS polymer roughened with chromic acid.

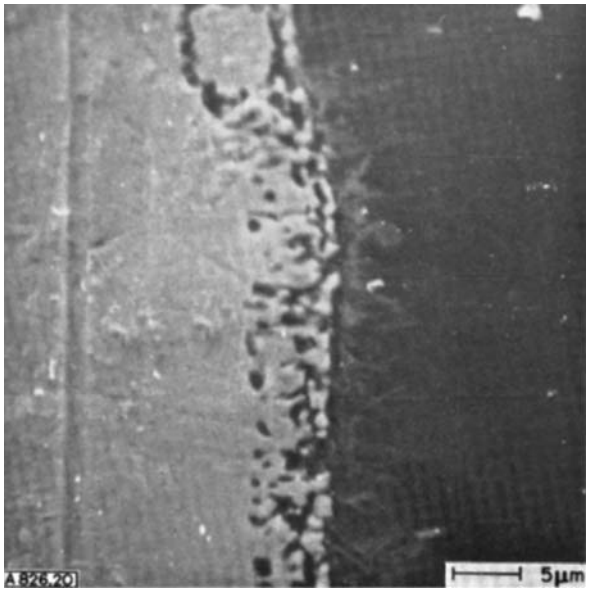


Fig. 20. Boundary between enamel (dark) and metal (bright). Polished section.

and organic materials[11]. Included in this class is the selective elimination of polybutadiene particles from ABS plastics with chromic acid (Fig. 19) as a pretreatment for electroplating[12]. Only the second class will be treated extensively in the following.

Of the interactions between electrons and solid in Fig. 3 only the emission of secondary electrons has been considered so far. However, the function of picture brightness control can also be assumed by backscattered, absorbed (sample current), or transmitted electrons (in thin films). In fact, we need not even confine ourselves to electrons—photons (in the cathodoluminescence mode) or electrical pulses generated by X-rays may serve the same purpose. The scanning principle is thus shown to be especially versatile; each interaction offers new possibilities for the imaging of surfaces or the recognition of material differences. In Fig. 3 no particular attention was paid to the Auger effect, which is treated in Section 3; the Auger electrons are included in the secondary electrons.

It has already been mentioned in Fig. 4 that in secondary electron images regions with heavy elements appear bright. Fig. 20 shows as an example a polished section (to avoid relief contrast) at right angles to an enamel/metal interface. The metal appears bright because of its higher atomic number, while the enamel appears dark. Between

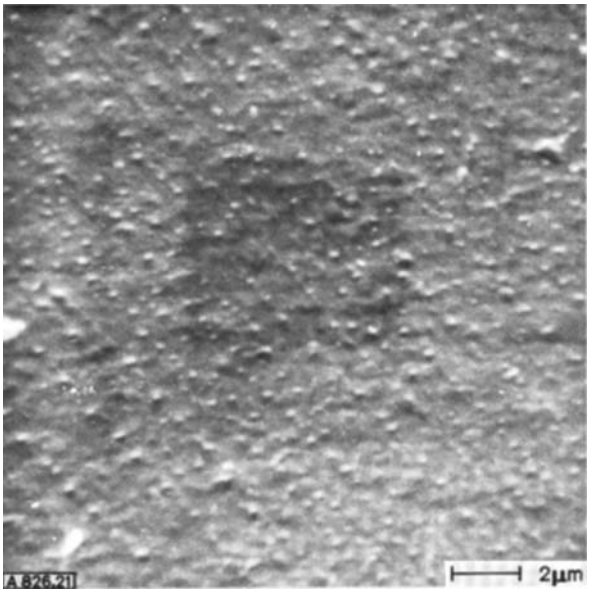


Fig. 21. Surface of a pigmented coating, primary beam voltage 5 kV.

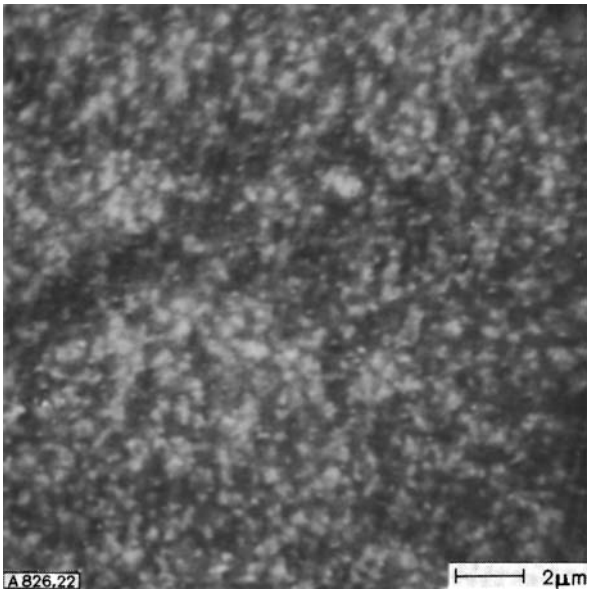


Fig. 22. Surface of a pigmented coating, primary beam voltage 20 kV.

them is the boundary, the involved structure of which guarantees good adhesion. There is a further effect in addition to the light-dark representation due to the difference in atomic number. This effect may be demonstrated on the example of a pigmented coating[13, 14]. Fig. 21 shows a coating surface which was imaged with 5 kV primary beam voltage. One can only see the pigments which protrude out of the coating surface. At 20 kV primary voltage the picture is entirely different (Fig. 22). A large number of indistinct bright spots predominates. These are pigments that lie below the surface; they are bright because of the difference in atomic number between the pigment and the other components of the coating, and indistinct because of the scattering processes suffered by the electrons within the coating. Thus the scanning electron microscope never images the mathematical surface of an object but "sees" a little way into the specimen[3a]. How deeply it sees it depends on the penetration power of the electrons, *i. e.* on the primary beam voltage and the density of the material under investigation.

If nature does not provide a sufficient difference in atomic number, in some cases it may be introduced by suitable preparation. In ABS plastics the polybutadiene phase can be stained with the aid of OsO_4. Thus the distribution of the polybutadiene *e. g.* in an injection-molded part can be made visible as the pigments in a coating[10] (Fig. 23; cf. also Fig. 19).

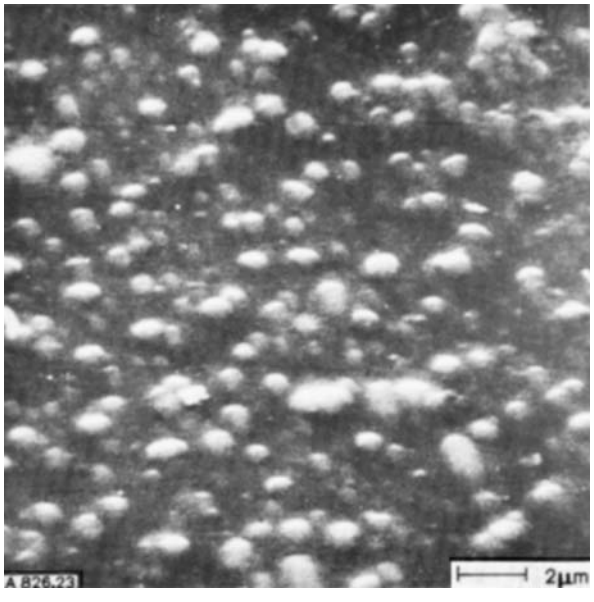


Fig. 23. Surface of an ABS injection-molded part after treatment with OsO_4.

The cathodoluminescence mode of operation allows an entirely different way of discriminating between materials. The emission of visible light during electron bombardment is well known from every cathode ray tube. However, the phenomenon is not confined to the inorganic compounds used there, such as crystalline zinc oxide or zinc sulfide, but is also exhibited by a range of organic dyes. Above all, the wide range of optical brighteners lends itself to a specific characterization of other organic substances. One thus obtains a method of discriminating between materials

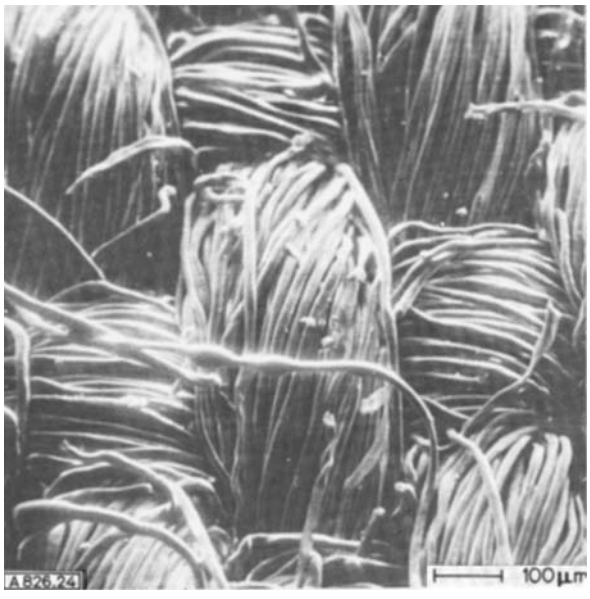


Fig. 24. Cotton-polyester mixed fabric after laundering test with addition of brightening agents. Picture using secondary electrons.

independently of the atomic number, in the purely organic field; a type of fluorescence microscopy with the depth of field of the scanning electron microscope can be carried out[14, 15].

The cotton/polyester mixed fabric shown in Fig. 24 was subjected to a laundering test. Only the cotton fibers picked up the brightening agent from the liquor. The difference between them and the polyester fibers cannot be detected in the secondary electron picture; on the other hand, with the cathodoluminescence technique (Fig. 25), the cotton fibers appear bright, whereas the polyester fibers appear as dark shadows.

It is often very difficult to demonstrate the presence of thin finishing agent films using secondary electrons. It therefore appears better to add brightening agents to the coating



Fig. 25. Cotton-polyester mixed fabric after laundering test with the addition of brightening agents. Picture using cathodoluminescence.

and apply the cathodoluminescence technique. As an example, consider the antifelting treatment of wool with Synthappret LKF®. Only the scales of the yarn should be stuck together to prevent felting (cf. Fig. 6). If the whole yarn is coated by the finishing agent, then the good properties of the wool as regards absorption and loss of water are lost. In Fig. 26 the required irregular distribution of

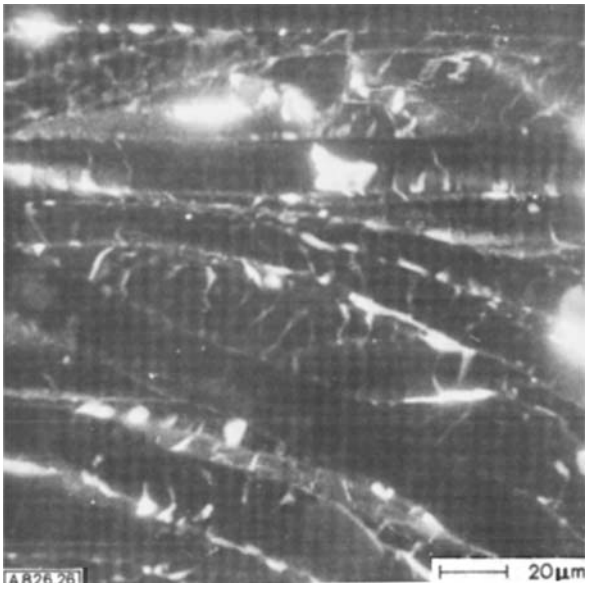


Fig. 26. Wool treated with Synthappret LKF® and brightening agent. Picture using cathodoluminescence.

the finishing and in particular the adhesion of scale edges have been made visible by the addition of a suitable brightening agent. Other examples of applications are the determination of the binder distribution in nonwoven fabrics, and the detection of faults in bleached fabrics. One problem is the destruction of the brightening agent by electron bombardment. Coumarin derivatives are more stable in this respect than stilbene derivatives.

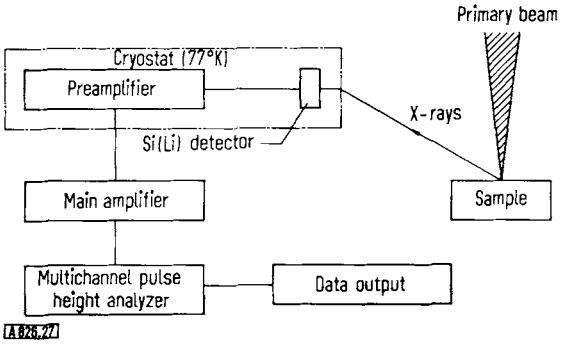


Fig. 27. Energy-dispersive X-ray spectrometer on the scanning electron microscope.

The interactions discussed so far only give material contrast and thus some indications for the analysis, not the elemental composition itself. This is made possible by the detection of the emitted X-rays. If the scanning electron microscope is regarded as an X-ray tube then the object under investigation plays the part of the anode. Since the beam currents in the scanning electron microscope are of the order of 10^{-10} to 10^{-12} A, the X-rays are not intense enough to allow analysis with crystal spectrometers within sufficiently short times. Energy dispersive analysis with the aid of solid-state detectors[16] is therefore better for the scanning electron microscope. Also, since semiconductor detectors cover a larger solid angle, they are preferable in the scanning electron microscopes to crystal spectrometers for geometrical reasons.

The system works on the following principle (Fig. 27): The semiconductor crystal transforms the X-rays into electrical pulses whose height is proportional to the energy of the incident X-ray quanta. These pulses are amplified, sorted, and stored in a multichannel pulse-height analyzer. After a few minutes of counting one obtains the energy spectrum of the characteristic X-rays of the elements in the region struck by the primary beam. The semiconductor industry can today supply lithium-drifted silicon detectors with an energy resolution of better than 200 eV; using these, it is possible to detect elements with atomic numbers $Z>11$ simultaneously and to distinguish between them.

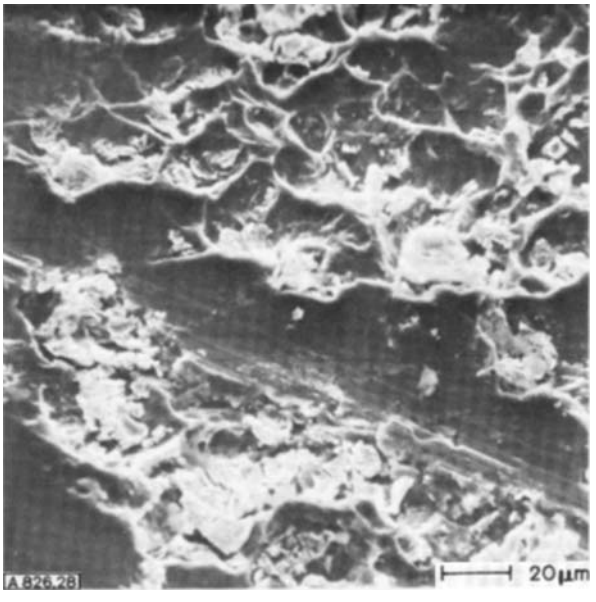


Fig. 28. Surface of a platinized titanium sheet. Picture using secondary electrons.

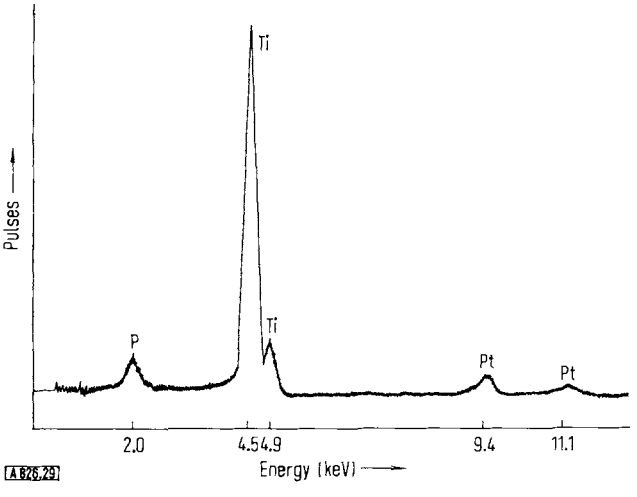


Fig. 29. Integral X-ray spectrum for Fig. 28.

At first sight the results from a scanning electron microscope resemble those of the microprobe (electron beam microanalyzer). Both devices make use of scanning, and both use the same interactions between electrons and solid for the analysis, in particular the emission of X-rays. The difference lies in the point of emphasis. The microprobe is an analytical apparatus; the imaging facilities serve largely for orientation while the analysis is being carried out, and for the representation of inhomogeneous element distributions. Hence, less emphasis is placed on the quality of the

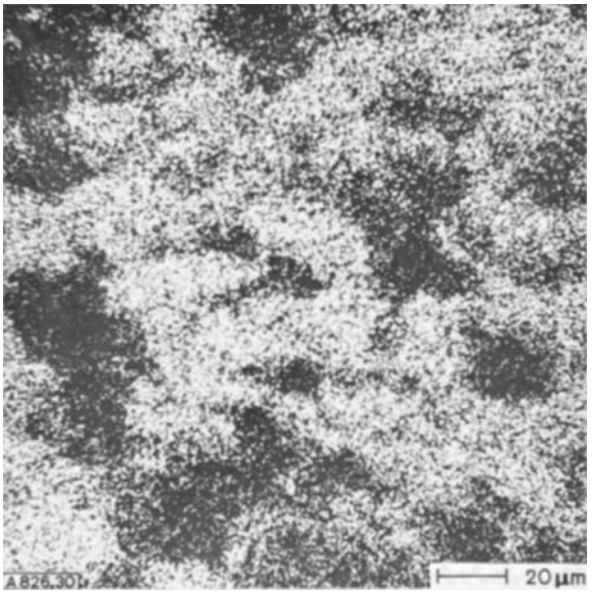


Fig. 30. Titanium distribution for Fig. 28.

imaging (the diameter of the primary beam is a few thousand angstroms) than on the extensive analytical possibilities: detection of light elements is possible as well, with high beam intensities (10^{-6} to 10^{-8} A) and a high spectral resolution in a crystal spectrometer. The scanning electron microscope, on the other hand, is first of all a microscope, and if the advantages of the low beam current and fine

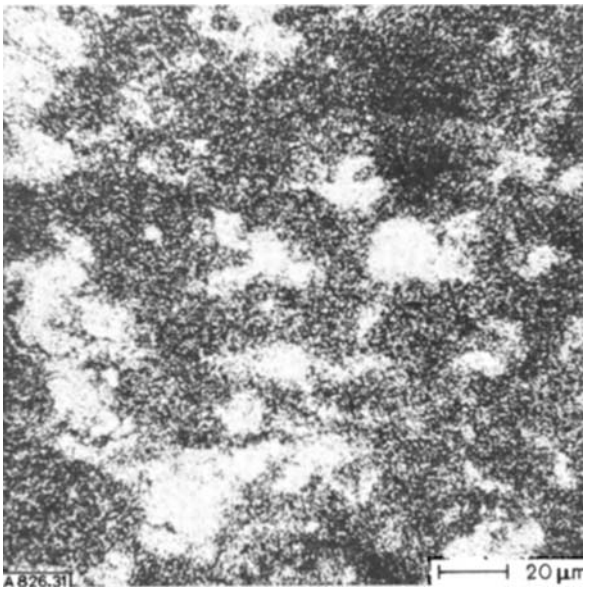


Fig. 31. Platinum distribution for Fig. 28.

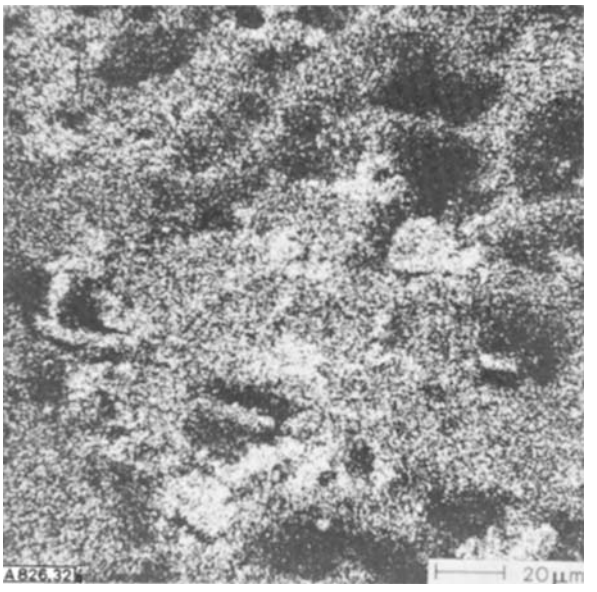


Fig. 32. Phosphorus distribution for Fig. 28.

focusing are to be kept, one is compelled to accept limitations in the analysis.

The information comes from a surface layer up to 20000 Å in thickness, depending on the penetration depth of the electrons. Since X-rays have a larger range in materials than slow electrons, X-rays may also come from deeper layers than those electrons by which the pigments in Fig. 22 were made visible. On the one hand, this can be exploited to analyze layers on or near the surface (with the possibility of varying the primary beam voltage); on the other hand, one cannot without further work conclude anything about the composition of the bulk from one spectrum.

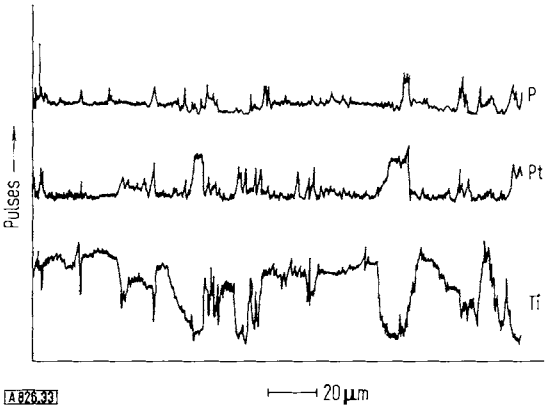


Fig. 33. Line scan for Fig. 28.

The detection limit of the scanning electron microscope for a homogeneously distributed element is about 0.1%; the process cannot therefore be considered as a method of trace analysis. The real advantage of its combination with an X-ray spectrometer lies in the possibility of investigating inhomogeneous distributions of elements at high spatial resolution and of carrying out a microanalysis. The spatial distribution of an element is displayed either in element pictures or in line scans. We start from the integral X-ray spectrum of an object region and choose

the energy interval in which the characteristic radiation of the desired element lies. In the element distribution picture the regions that emit X-rays of the selected energy appear bright. In the line scan the abundance of an element is plotted along a line.

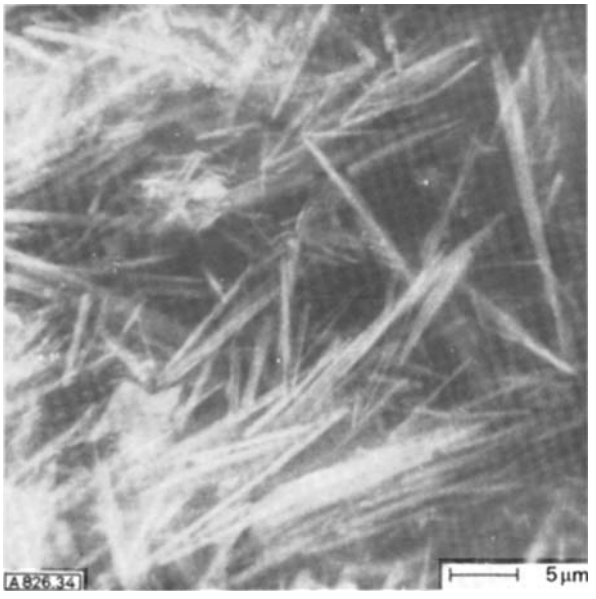


Fig. 34. Section from a spot in faulty PVC sheet.

Fig. 28 shows the surface of a platinized titanium sheet that had been used as a catalyst. From the X-ray spectrum (Fig. 29) one can deduce the presence of titanium, platinum, and phosphorus. The element distribution diagrams (Figs. 30 and 31) are complementary to one another and confirm the expectation that platinum and titanium will appear bright and dark respectively in the secondary electron image. Phosphorus appears above all on the edge of the platinum regions (Fig. 32); this cannot be seen in the secondary electron image (Fig. 28). The same information can be obtained from the line scan in Fig. 33. The material was analyzed along the line indicated by the arrows in Fig. 28.

The scanning electron microscope in combination with an X-ray system is suitable for easy identification of pigments, fillers, or dirt in polymers, alloys, enamels, *etc.* White

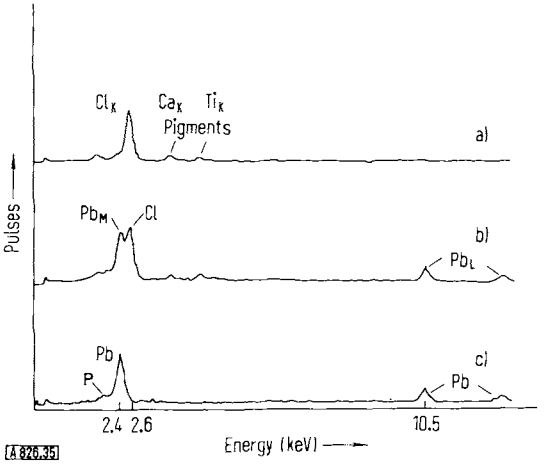


Fig. 35. X-Ray spectrum for Fig. 34.
(a) Normal region; (b) white needles (thin film); (c) center of white speck.

specks were found in a blue-colored PVC sheet and with higher magnification these were seen to contain needle-shaped crystals (Fig. 34). The X-ray spectrum (Fig. 35) indicates lead and phosphorus. Such a salt of lead was added to the PVC as a stabilizer, but it was poorly dispersed. Precipitates were found in the fracture surface of an austenitic steel (the spherical deposits in Fig. 36) and could easily be analyzed with the aid of the X-ray system (Fig. 37).

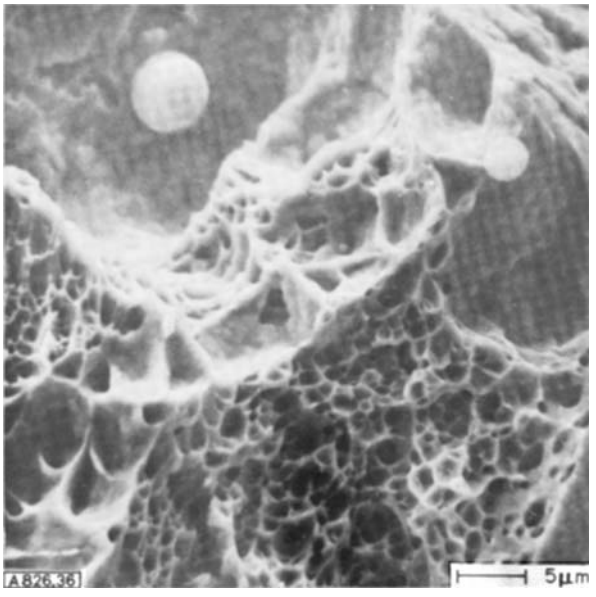


Fig. 36. Fracture surface of an austenitic steel with inclusions.

The investigation of a surface under a scanning electron microscope has certain limitations that cannot be overcome with a combined system for imaging *and* analysis. On the one hand, the spatial resolution of the scanning electron

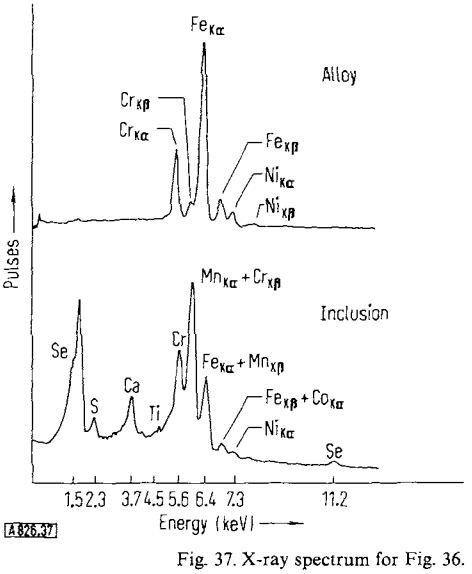


Fig. 37. X-ray spectrum for Fig. 36.

microscope is only 100—200 Å. A higher resolution (down to a few angstroms) can only be achieved by investigating a replica under the transmission electron microscope; this means, however, that the possibilities for material differentiation and analysis are lost. On the other hand, the X-ray detector can only cover elements with an atomic number

$Z > 11$. The detection of lighter elements as well can only be achieved at the expense of the imaging properties (microprobe). Basically, one obtains only an analysis of the elements, and no information on the compounds formed from them. On the other hand, the information from a scanning electron microscope (no matter whether it is a surface image or an element distribution picture) comes from a surface layer which is 1000—20000 Å thick; typical surface effects, which occur in layers less than 100 Å thick, are therefore lost because of intensity problems. Surface analysis methods provide further information, but they are not localized methods.

At the present time there are only two methods of surface analysis that comply with the additional requirements of versatility and easy application: secondary ion mass spectroscopy[17] and photo- and Auger electron spectroscopy[18], which should be regarded as a supplement to scanning electron microscopy.

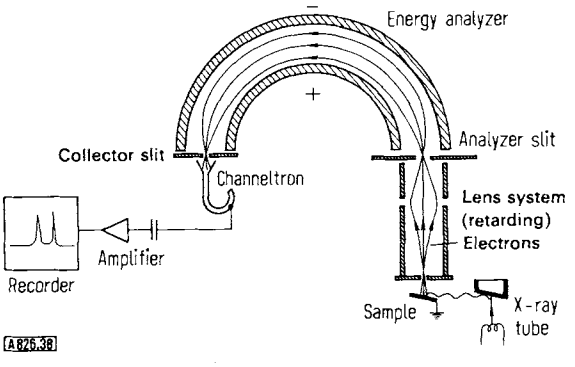


Fig. 38. Block circuit diagram of an electrostatic electron spectrometer ("ES 100", AEI Manchester).

By the term electron spectroscopy we mean here the measurement of the kinetic energy of electrons emitted by a substance on irradiation with UV light, X-rays, or electrons. We shall limit ourselves here to the investigation of solids and excitation with X-rays. *K. Siegbahn* gave the name ESCA (electron spectroscopy for chemical analysis) to this special case. Fig. 38 shows the block diagram of a modern electrostatic electron spectrometer. X-rays (*e.g.* $Al_{K\alpha}$, $Mg_{K\alpha}$) are directed at the specimen; the kinetic energy of the electrons emitted from the surface is then measured with the aid of a spherical condenser; a Channeltron serves as the detector. All solids and substances that can be condensed at -150 °C can be investigated in this way. The measurement requires a vacuum of better than 5×10^{-6} torr.

Electron spectroscopy is based on the photoelectric and the Auger effect (Fig. 39). An X-ray quantum of energy $h\nu$ may have sufficient energy to liberate an electron from the K shell of an atom with ionization energy E_K. The electron thus liberated has then a kinetic energy

$$E_{kin} = h\nu - E_K$$

After this primary process there are two possible relaxation processes for the excited atom. On the one hand, an electron, of, *e.g.*, the L_{III} shell can fill up the hole in the K shell, the energy released in the process being radiated as a $K\alpha_1$ line (X-ray fluorescence). If this energy is greater than the ionization energy of an L electron, the energy can also be transferred within the atom without the occurrence of radiation to a second electron which is emitted (Auger effect). To estimate the kinetic energy of the Auger electron we may proceed as if the X-ray quantum liberated by the transition of an L_I electron into the K shell were to ionize the L_{III} shell. The kinetic energy of the emitted L_{III} electron is then

$$E_{kin} \approx E_K - E_{L_I} - E_{L_{III}}$$

It is important to note that ESCA reproduces directly the electronic level of the atoms involved in the photoelectric or Auger effect. The position of the energy levels can be calculated unambiguously from the recorded spectra.

Whether X-ray fluorescence or the Auger effect is more probable depends on the atomic number of the element. As shown in Fig. 40, for the lighter elements the Auger effect is significantly more probable than X-ray fluorescence. This explains the difficulties in detecting light elements when using the X-ray spectrometer on the scanning electron microscope. Since the photoelectric and the Auger effect occur in all elements, electron spectroscopy is applicable with nearly the same sensitivity to all elements and is not subject to the limitations of say X-ray fluorescence which is only practicable for elements with $Z > 11$.

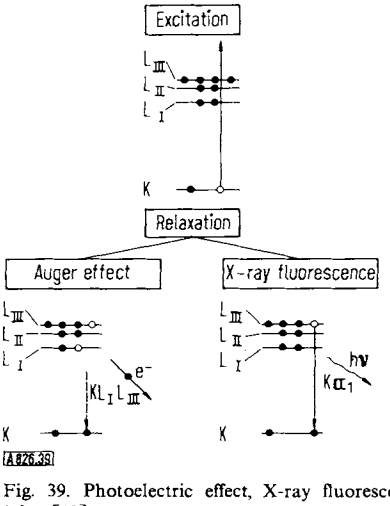


Fig. 39. Photoelectric effect, X-ray fluorescence, and Auger effect (after [18]).

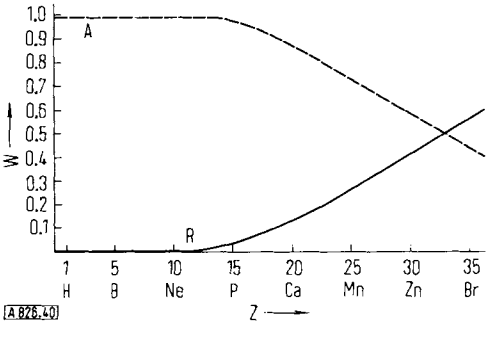


Fig. 40. Probabilities (W) of X-ray fluorescence (R) and Auger effect (A) (only for K and L shells) (after [18]).

Exceptions are hydrogen and helium, which have only one electron shell.

On passing through matter electrons lose energy, these losses being not continuous but quantized (excitation of plasmons of surface and volume type)[19]. This point is demonstrated by the fact that in the electron spectrum a line is always accompanied by a satellite (more or less continuous energy distribution) on the side of lower kinetic energy; the line is separated from this satellite by at least one minimum (cf. Fig. 41). This minimum is of fundamental importance because one can be sure of having in the principal line only those electrons that have not lost any energy, corresponding to the O-phonon transition in the Mössbauer effect. Of course, only those electrons can contribute to this line that come from the uppermost monolayers. Hence electron spectroscopy constitutes a suitable method of investigating surfaces.

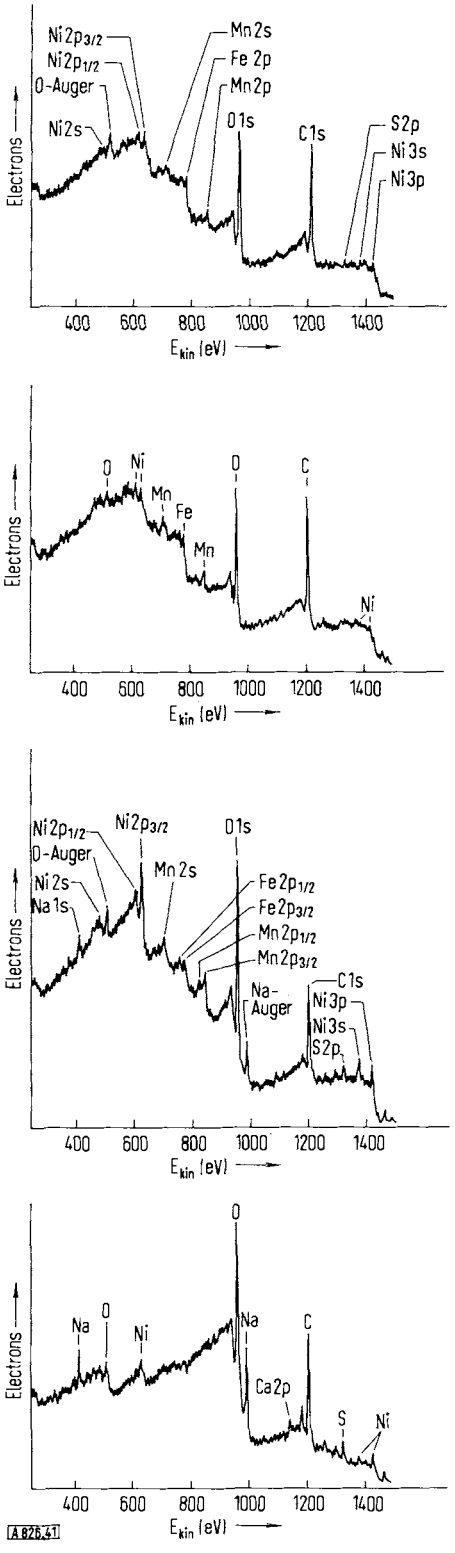


Fig. 41. ESCA, overall spectra of steel surfaces pretreated in various ways.

The width of the lines in the electron spectrum is 1—2 eV. There are contributions from: 1) the natural line width of the level under investigation, and 2) the width of the incident X-ray line. The energy level shifts of an atom under the influence of neighboring atoms (chemical bonds, hydrogen bridges, van der Waals forces, crystal effects, *etc.*) are up to 10 times as large. Detection of such shifts gives the possibility of contributing to the determination of the structure of inorganic and organic molecules. Information is obtained on the electron density in the environment of the nucleus and it is possible to make deductions regarding the oxidation state and valence. In electron spectroscopy the shifts are measured directly, while in X-ray fluorescence, for example, only the difference between the shifts of two terms is susceptible to measurement.

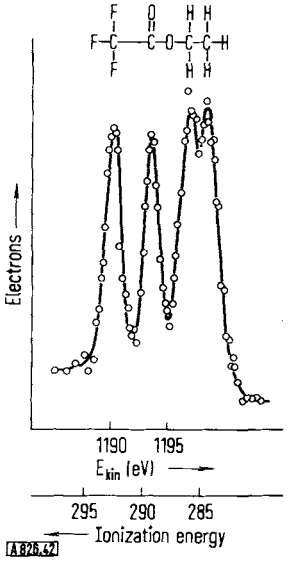


Fig. 42. C1s photoelectron spectrum of ethyl trifluoroacetate (after [18]).

The order of magnitude of chemical shifts is evident from the C 1s photoelectron spectrum of ethyl trifluoroacetate, the example quoted by *K. Siegbahn* (Fig. 42)[18]. If some charge is partly removed from an element participating in a polar bond, then the remaining electrons are more tightly bound to the nucleus. This is made evident in the higher ionization energy and in the electron spectrum by a lower kinetic energy of the photoelectrons. For this reason the C 1s line of carbon in the CF_3 group appears at lower kinetic energies than the C 1s line of carbon in the CH_3 group.

The overall region of observed shifts is, however, too small in comparison with the line width to allow replacement of other spectroscopic methods for structure investigation by ESCA. The ratio of the maximum shift to the halfwidth is of the order of 10; an analogous ratio for *e.g.* nuclear

magnetic resonance is greater than 1000. The disadvantage of the lower selectivity is in general not removed even by the advantage of having a way of studying bond effects in all the partners involved.

The situation is different in surface analysis. In this case every indication going beyond elemental analysis is useful information about surface compounds that cannot be obtained in any other way. It has already been pointed out in connection with Fig. 41 that the information from an ESCA spectrum is derived from the uppermost atomic or molecular layers. The mean escape depth of the photoelectrons is about 20—30 Å[20], for an energy of 1200 eV. Hence electron spectroscopy is to a much greater extent than scanning electron microscopy a method of surface analysis. However, an escape depth of 30 Å means that not only the first monolayer of atoms is analyzed. For routine applications this has the advantage that one does not need ultrahigh vacuum, since although a low absorption of residual gas causes a loss of intensity, it does not otherwise hinder the measurement. The relatively large escape depth of photo- and Auger electrons becomes evident for instance in the fact that in metals stored in air one obtains mostly a doublet for each line. The electrons with the lower kinetic energy come from the oxide (or hydroxide) layer; the electrons with the higher kinetic energy come from the metal lying below it. Fig. 43 shows the $4f_{5/2}$ and $4f_{7/2}$ photoelectron spectra of tungsten sheets oxidized to different extents. If one knows the escape depth for the kinetic energy involved, such a spectrum can reveal the thickness of a passivation layer as well as its composition.

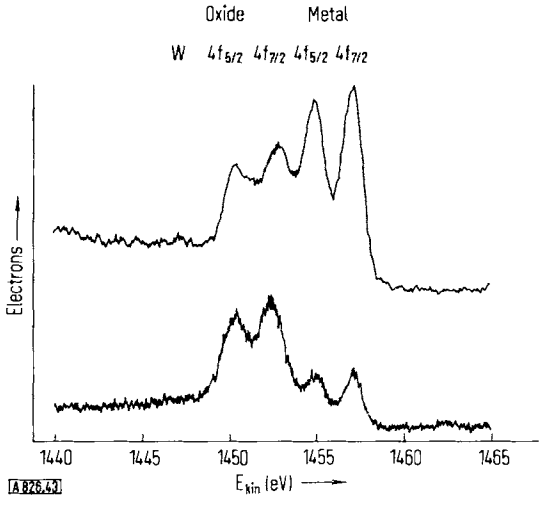


Fig. 43. W4f photoelectron spectra of variously oxidized tungsten sheets.

Further fields of application are found in catalysis, in the analysis of absorption layers, and in the investigation of pretreatments of foils or sheets (cf. Fig. 41; the differences are not evident in the X-ray spectrum, since they involve only very thin surface layers), in corrosion protection, in electroplating, or in the analysis of finishing coatings on fibers. Fig. 44 shows the analysis of a coupling agent of the aminosilane type on glass fibers. For the effect of a coupling agent, see Figs. 17 and 18. From the overall spectrum (Fig. 44 above) one can tell which elements are present. The regions for C 1s and N 1s were recorded again (at a different spectrometer sensitivity) with an expanded abscissa. Comparison measurements yield the energy positions, the line widths, and line shapes of the C 1s levels for carbon atoms in various compounds. It follows in our example from the

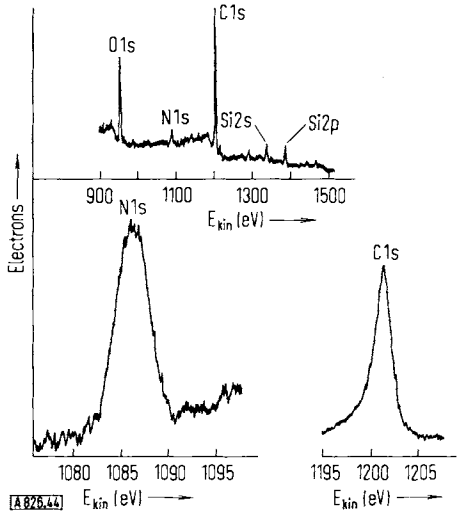


Fig. 44. Electron spectrum of a coupling agent on glass fibers.

asymmetry of the C 1s line (left flank) that not only C—H bonds but also, to a smaller degree (about 20%), C—O bonds (C—OH or ester bonds) are present. As the line shape is well reproducible it is possible to use graphical or

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computer deconvolution. The broad N 1s line also indicates that nitrogen does not occur only in one state of binding.

Since the Auger effect can also be excited by electron bombardment, the question arises whether it may be possible to couple the scanning electron microscope and an electron spectrometer. For commercial scanning electron microscopes this is not practicable because of the poor vacuum. The pressure must be lowered to at least 10^{-8} torr, otherwise only contamination layers will be analyzed. This will happen particularly in the case of Auger lines of low kinetic energy since the escape depth is then also reduced. The Auger effect can in fact be observed on operation of a scanning electron microscope at an improved vacuum (ion getter pumps, metal seals) and it has already been utilized in surface analysis of metals[21].

Difficulties arise in the case of insulators due to electrostatic charging. There is the additional danger of destruction of the surface layer by intense electron bombardment, which is greater than the possible damage by X-rays. Measurement of chemical shifts is feasible only with sharp Auger lines. The large line width frequently observed stems from the width of the outer energy level from which the Auger electron is usually liberated. Thus a combination of electron microscope and electron spectrometer is possible in principle; in practice, however, such a system will be used only for those problems which require surface analysis with high spatial resolution and which cannot be solved by X-ray fluorescence methods.

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Reactions of Atoms

By Heinz Georg Wagner and Jürgen Wolfrum[*]

Several methods for the quantitative investigation of reactions of free atoms in the gas phase have been developed in recent years. The present article deals with reactions of hydrogen, carbon, oxygen, and halogen atoms with simple molecules. The results of such investigations are of fundamental importance for the understanding of chemical reactions and for many technical applications, such as explosion and combustion processes, halogenations, and chemical lasers.

1. Introduction

Reactions of atoms are among the simplest of chemical processes. They offer favorable conditions for a quantitative theoretical treatment and demonstrate many properties typical of neutral particle reactions. These properties include not only the rate constants and the apparent (Arrhenius) activation energies, but also information about the activated complex, the "rearrangement" of the reactants during the reaction process, and the probabilities of various reaction pathways, *i.e.* the formation of various reaction products, the distribution of the reaction energy over the products, *etc.* In addition, the influence of electronic excitation and high kinetic energy of the reactants can also be readily investigated for atoms.

From the practical side the use of fast reactions of free atoms and radicals for the production of energy from combustion processes is one of the oldest of all chemical techniques. It has recently become increasingly clear that the rapid expansion of the use of combustion processes has reached a point such that the natural atmosphere is already being considerably affected. A thorough knowledge of the elementary steps taking place in explosion and combustion processes (see *e.g.* Sections 2 and 4) is therefore not only necessary in order to extract the maximum energy from the reaction process, but is also essential to the success of efforts to suppress the formation of undesirable products such as CO, NO, O_3, and the incomplete combustion of the hydrocarbons used. The reactions of free atoms also play an important part in many photochemically or radiation-initiated processes such as occur in the atmosphere or in industrial applications (*e.g.* reactions of halogen and hydrogen atoms with hydrocarbons; see Sections 2.4 and 5.3). The intensive study of atomic reactions recently led to the discovery of the chemical laser. The chemical laser, which is still in the early stages of its development, shows promise of interesting applications *e.g.* in the production of plasmas, for the probable initiation of controlled nuclear fusion, and for the solution of numerous technical problems. Some atomic reactions that are important to chemical lasers will be described (see Sections 2.2 and 5.1).

It has been known for a long time that even careful analysis of the stable starting materials and end products of a chemical reaction usually gives only limited information concerning the individual reaction steps. Efforts must therefore be made to isolate these elementary steps from the overall reaction. At temperatures of a few thousand degrees Kelvin, at which the atoms in question exist in appreciable concentrations in thermal equilibrium with

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stable molecules, only a few collisions are usually necessary for further reaction of the atoms (reaction times at atmospheric pressure 10^{-8}—10^{-7} s). At lower temperatures (200—1000 °K) and reduced pressure (a few torr), however, the reaction times become easily measurable (10^{-3} to 10^{-1} s). Methods of producing atoms under such conditions have been known for a long time, *e.g.* in the form of electric discharge or photolysis. It is only during the last few years, however, that reliable quantitative results have become obtainable in this way through greatly improved analytical techniques for the accurate determination of atoms and radicals. These include various spectroscopic methods, such as electron spin resonance and mass spectroscopy, as well as the sensitive detection of chemiluminescence or resonance fluorescence in the presence of atoms. Detection of individual atoms was achieved for the first time on the basis of surface ionization (Langmuir-Taylor detector) for alkali metal atoms, whose reactions with halogen compounds could be investigated in great detail in crossed molecular beams. This method probably provides the most detailed information on the microscopic course of a chemical reaction of neutral particles. Some typical findings for reactions of alkali metal atoms have recently been described[1]; a detailed description may be found *e.g.* in [2–4].

Molecular beam scattering experiments with other types of atoms have now also been reported[5], but few results are available as yet for the atomic reactions in the H-C-N-O system which are of great practical importance. Molecular beam studies will therefore not be discussed further in this progress report, which will deal instead with recent results for reactions of hydrogen, carbon, oxygen, and halogen atoms[*] with simple molecules, including the investigation methods used. The selection of the examples is naturally rather limited and arbitrary; however, very comprehensive collections of the known rate constants of elementary reactions have already been published[6–9].

2. Hydrogen Atoms

2.1. Reaction with H_2

The exchange reaction of hydrogen atoms with hydrogen molecules is the classic textbook example of an atomic reaction, and indeed this reaction fulfills better than any other the prerequisites for a complete theoretical treatment of a elementary chemical process. The first experimental and theoretical studies with this aim were carried out more than 40 years ago, but for a long time the cause of the discrepancy found was uncertain. It is only recently that advances have been made in both fields which allow a meaningful quantitative comparison of the results.

Figure 1 shows an Arrhenius plot of recent results[10–18] from experiments (points) and calculations (continuous lines) for the rate constant of the reaction

$$D + H_2 \longrightarrow HD + H;\ \Delta H_0^\circ = -0.8\ \text{kcal mole}^{-1} \qquad (1)$$

[*] Reactions of N atoms and excited N_2 molecules have been described by *G. R. Brown* and *C. A. Winkler*: Angew. Chem. *82*, 187 (1970); Angew. Chem. internat. Edit. *9*, 181 (1970).

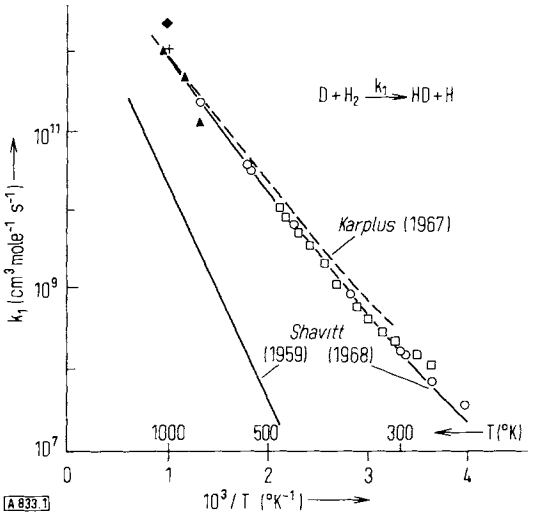


Fig. 1. Calculated (curves) and measured (points) rate constants for the reaction $D + H_2$.
□ [10], ○ [11], + [12], ◆ [13], ▲ [14]; —— [16, 17], - - - [18].

It is clear that the direct observation of the reaction (empty circles and squares) covers a much wider temperature range and gives more accurate values for the rate constant than earlier measurements (shaded points), in which only the overall reaction

$$H_2 + D_2 \longrightarrow 2HD$$

could be investigated.

Figure 2 shows an apparatus for direct measurement of the rate constants of reaction (1) and of other atom-molecule reactions. It consists of a flow system connected to an electron spin resonance (ESR) spectrometer and a mass spectrometer[19].

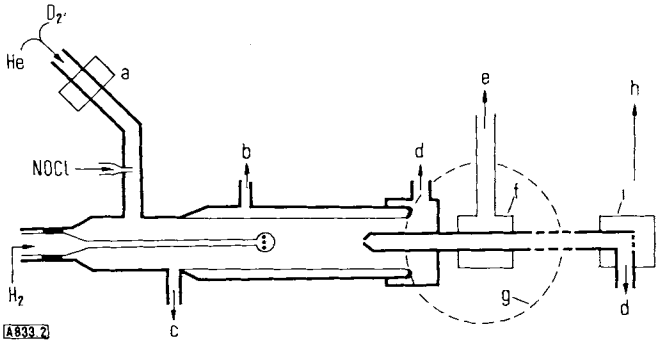


Fig. 2. Flow system for the direct investigation of atom-molecule reactions [19].
The quartz flow reactor can be heated to temperatures between 200 and 1100 °K by means of a thermostat (b) or a furnace. The gases to be dissociated (in this case D_2) pass through a side arm in a carrier gas (helium or argon), into an electrodeless microwave discharge (a: power 50—200 W). Stable reactants (in this case H_2) are mixed with the atoms through a mobile inlet at various points in the flow reactor (mixing time 10^{-3} s). The total pressure (c: manometer, d: pump) is usually between 2 and 10 torr, the reaction times are $\approx 10^{-2}$ s, and the lifetimes of the atoms for recombination on the wall, with suitable treatment of the vessel walls (*e.g.* rinsing with 5% HF solution), is 1—0.1 s. Because of the low concentration of atoms (partial pressure of the atoms 10^{-2} to 10^{-3} torr), no appreciable recombination of the atoms with one another takes place during the reaction time. Gas samples are taken from the flow reactor by means of a quartz probe, and are allowed to expand to 0.1 torr and are then rapidly pumped through the resonator (f) of the ESR spectrometer (e) (g: magnetic pole). Atoms can be quantitatively detected here even at a partial pressure of 10^{-5} torr. Stable components (after recombination of the atoms on the wall) can then be analyzed *e.g.* by means of a mass spectrometer (h) or a gas chromatograph (i: ion source).

Whereas only nonspecific methods for the detection of atoms (measurement of the heat of recombination of the atoms on metal surfaces, Wrede-Harteck gauge) were available during the classic experiments of *Wood* and *Bonhoeffer*, a precise, specific detection of the atoms is now possible by ESR spectroscopy (the atoms absorb on the basis of differences in line splitting at various magnetic field strengths). Atomic H-D exchange processes such as reaction (1) can readily be observed by this method.

Not only experimental measurements but many purely theoretical calculations of rate constants have also been attempted. The basis of such calculations is a precise knowledge of the forces acting between the reactants during the reaction. These forces can be represented by one or (if a change in the electronic state occurs during the reaction) by several "potential energy surfaces", which give the potential energy of a molecule[*] as a function of the positions of all the atoms for a given electronic state. For a diatomic molecule, they correspond to the well-known potential-energy curves with only one internuclear distance parameter, while for a triatomic molecule already three

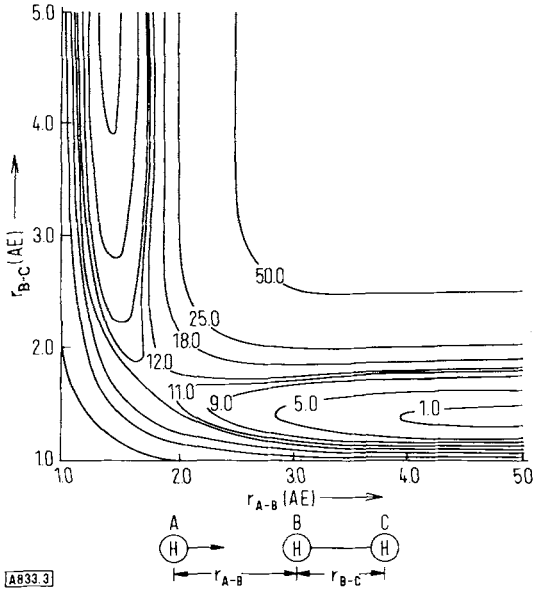


Fig. 3. Quantum-mechanically calculated potential-energy surface for the reaction $H+H_2$ [20]. Contour lines in kcal mole^{-1}, internuclear distances in atomic units (1 AU = 0.52 Å).

distances have to be considered. The situation is simplified if in the reaction between an atom and a molecule, one considers only the case in which the reacting atom (A) collides at a constant angle with the molecule (BC). The potential energy of the "molecule" ABC then depends only on two distances (r_{A-B}, r_{B-C}), and can be represented as an energy "contour map". Figure 3 shows such a map for the reaction[**] $H+H_2$[20]. It was calculated quantum-mechanically without the aid of experimental information and taking into account the interaction of a total of 15 orbitals (1 s, 1 s', 2 p_x, 2 p_y, 2 p_z for each H atom). In contrast with earlier calculations, there is no indication of a stable H_3 complex, *i.e.* a potential well at the saddle point.

[*] In the case of a reaction, all the particles are considered together as a sort of "supermolecule".

[**] For the reaction $H+H_2$, the energy barrier is lowest for the collinear approach.

The rate constant of reaction (1) can now be obtained in two quite different ways using the potential-energy surface. One method is to apply transition state theory[21], for which the properties of the activated complex and the height of the potential-energy barrier E_c[*] are derived from the potential-energy surface. Only a small part of the entire surface, that surrounding the saddle point, is needed for this calculation[**].

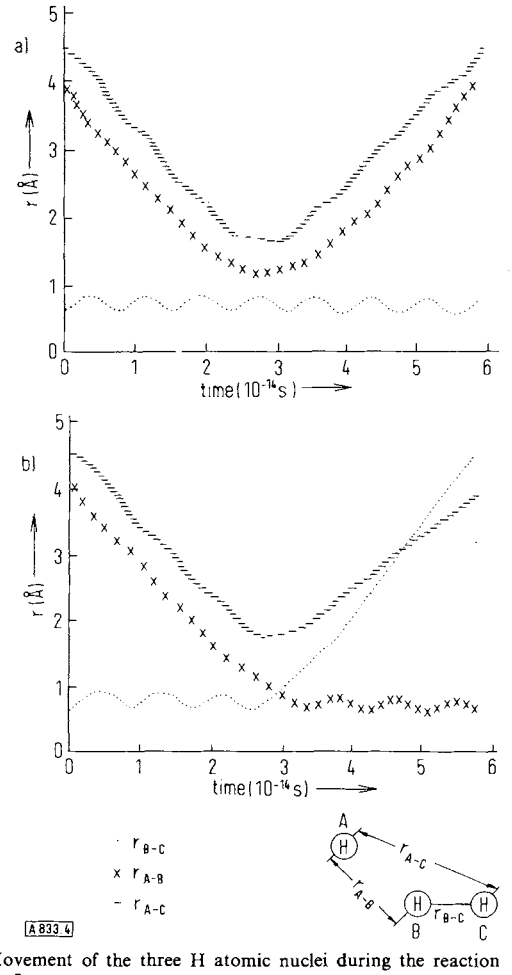


Fig. 4. Movement of the three H atomic nuclei during the reaction $H+H_2$ [23].

Figure 1 contains the results obtained in this way by *Shavitt* for the reaction (1). An energy surface calculated quantum-mechanically by *Boys* and *Shavitt*[15], which takes into account only the interaction of a total of 6 orbitals (1 s, 1 s' for each H atom), was used initially for this purpose; the potential-energy barrier obtained was too high ($E_c = 15.4$ kcal/mole), with the result that the agreement with the experimental data was unsatisfactory[16]. Much better agreement is obtained[17] by the use of the surface shown in Figure 3, where a total of 15 orbitals were taken into account in the calculation.

An entirely different method was used by *Karplus et al.*[23]. Instead of considering the H_3-complex, these authors

[*] A discussion of the relationships between the potential-energy barrier (E_c), the threshold energy (E_0), and the experimental Arrhenius activation energy (E_{exp}) may be found in [22].

[**] Within the Born-Oppenheimer approximation the shape of the potential-energy surface does not change when one considers the reaction $D+H_2$ instead of $H+H_2$. However, the difference in the zero-point energies of the H_3 and DH_2 complexes must be taken into account.

followed the movement of three H atoms on the potential-energy surface by stepwise integration of the classical equations of motion. Two examples are shown in Figure 4. The distances between the three atoms involved are plotted as a function of time. In one case (Fig. 4a), no reaction takes place on collision of the H atom (A) with the H_2 molecule (BC); the H_2 molecule exhibits an undisturbed zero-point vibration. The second diagram (4b) shows that a reaction has taken place; the molecule AB has been formed, and the atom C is moving away from AB. Calculations of this type have been carried out for various starting conditions (relative velocities, orientations of the collision partners, and rotational states of H_2). Suitable averaging over a Maxwell-Boltzmann distribution of the starting conditions of the reactants gives the picture shown in Figure 1 for the macroscopic rate constant k_1 as a function of temperature.

The agreement with the experimental data is good at higher temperatures. This substantially classical treatment can no longer be applied at lower temperatures ($T < 300\,°K$), since quantum mechanical tunneling must then be taken into consideration[24, 25].

2.2. Reactions with Halogens

The reactions of hydrogen atoms with Cl_2 and Br_2 play an important part as chain steps in the chlorine- and bromine-hydrogen reaction. The rate constants of these reactions have been known for a long time. *Tal'roze et al.*[26] were recently also able to study the reaction of H atoms with F_2 directly. The rate constants of the four reactions

$$H + F_2 \longrightarrow HF^* + F;\quad \Delta H_0^0 = -98\,(101)\ \text{kcal mole}^{-1}\ [27, 28] \quad (2)$$

$$H + Cl_2 \longrightarrow HCl^* + Cl;\quad \Delta H_0^0 = -45\ \text{kcal mole}^{-1} \quad (3)$$

$$H + Br_2 \longrightarrow HBr^* + Br;\quad \Delta H_0^0 = -30\ \text{kcal mole}^{-1} \quad (4)$$

$$H + I_2 \longrightarrow HI + I;\quad \Delta H_0^0 = -19\ \text{kcal mole}^{-1} \quad (5)$$

are shown in Figure 5[*]. The reactions are all very fast, but it should be noted that reaction (2), which is the most strongly exothermic, proceeds much more slowly than the reactions (3), (4), and (5)[**].

These reactions have recently attracted renewed attention. It was found that the hydrogen halide molecules formed exhibit strong vibrational and rotational excitation, which is manifested in chemiluminescence in the infrared region. By observation of this emission, *Polanyi et al.*[36] found *e.g.* for reaction (3) that approximately 45% of the available reaction energy is converted into vibrational energy of the resulting HCl* (with 1 to 6 vibrational quanta). The distribution of the rotational energy also exhibits pronounced deviations from the equilibrium population (maximum at $J = 12$).

This experimentally determined distribution of the reaction energy over the reaction products provides an insight into the shape of the potential-energy surface that determines the reaction, and also pointed to an interesting possibility of converting chemical energy into radiation energy in a chemical laser.

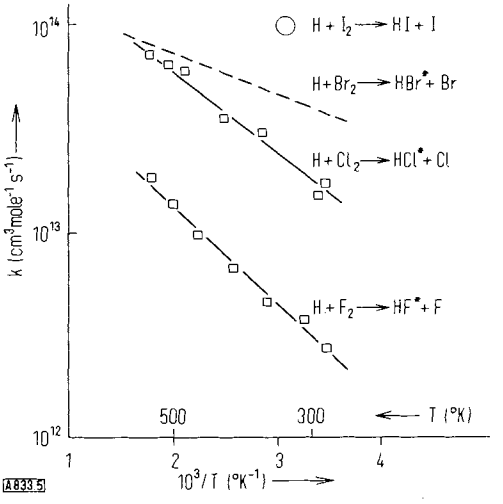


Fig. 5. Rate constants for the reactions of hydrogen atoms with halogen molecules.
□ [26], ○ [31, 32]; --- [29, 30].

The relationship between the shape of the potential-energy surface and the vibrational excitation of the reaction products will be described with the aid of Figure 6.

Two different potential-energy surfaces are shown for the reaction between an atom (A) and a molecule (BC). The linear arrangement of A and BC is again chosen for the sake of simplicity. The approach of A to BC, *i.e.* the decrease in the distance r_{A-B}, corresponds in the contour diagram to the movement of a point along the indicated line ("reaction coordinate") in a valley from right to left. In the first case (Fig. 6a), the point moves uphill, and with increasing height, the path of least potential energy leads increasingly in the y direction, *i.e.* a decrease in r_{A-B} is associated with an increase in the distance r_{B-C} between the atoms in the molecule BC. If the kinetic energy of the collision partners is sufficient, the pass is finally crossed. The point then moves rapidly downward into a valley, which, in an exothermic reaction, is lower than the starting valley by an amount that corresponds to the heat of reaction. The distance between the new molecule AB and the atom C increases without causing any change in the distance r_{A-B}, *i.e.* without stimulating vibration of the product molecule AB. The heat of reaction is liberated in this case only at a very late stage, *i.e.* near the end of the reaction path.

A different picture is obtained if the reaction proceeds on a potential-energy surface of the form shown in Figure 6b. The approach of A corresponds to the movement of a point from right to left in a shallow valley, *i.e.* only a small energy barrier, if any, has to be overcome in the reaction. The valley then suddenly falls away steeply, so that the

[*] The reaction enthalpies, unless otherwise indicated, were calculated from JANAF thermochemical tables (Dow Chemical Company, Midland, Mich. 1965; first addendum 1966).

[**] The example shows that the type of reaction must be taken carefully into account in the application of the empirical rule of *Polanyi et al.* [33, 34], which states that the activation energy in a homologous series of exothermic elementary steps of the type $A + BC \rightarrow AB + C$ decreases for the most strongly exothermic reactions. The rule fails if two atoms or characteristic groups are varied within the homologous series. This is so in reactions (2)—(5) (simultaneous variation of B and C) [35].

point moves rapidly downward, and very small distances r_{A-B} are reached, *i.e.* the atom A is "drawn" by B and can therefore move closer to B than the equilibrium distance in the product molecule AB. The further movement shows that in this case the increase in the distance between the new molecule AB and the atom C is associated with a simultaneous periodic change in the distance r_{A-B}, *i.e.* with stimulation of vibration of the product molecule AB.

These examples illustrate two extreme cases, between which the potential-energy surfaces constructed quantum-mechanically (*"ab initio"*) or by semiempirical methods may be modified for a given reaction until agreement is reached between the experimental and calculated distributions of the energies in the reaction products. For calculations on reaction (3), see [37–39].

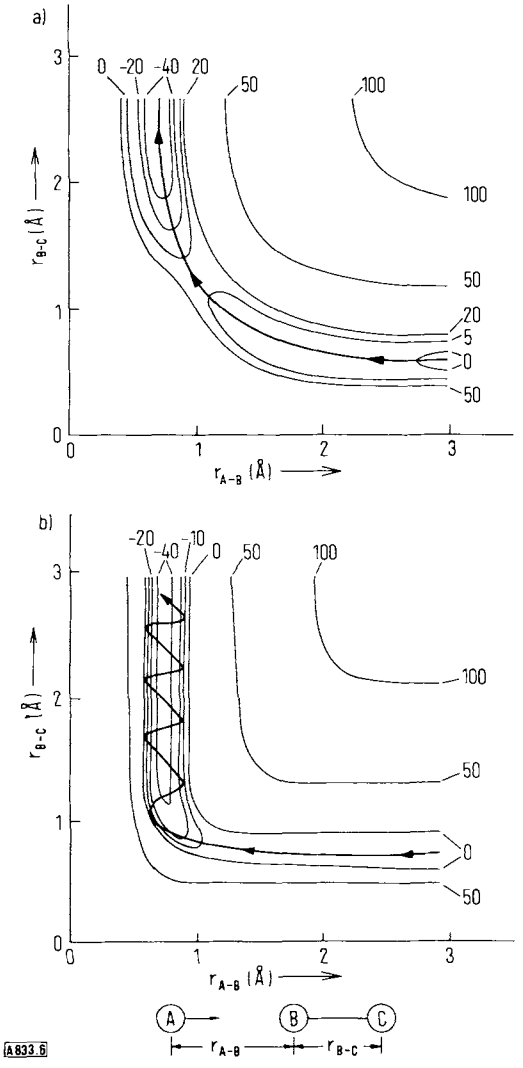


Fig. 6. Relation between the shape of the potential surface and the vibrational excitation of the product molecule for an exothermic reaction A + BC → AB + C. Energy contours in kcal mole^{-1}.

Reaction (3) was also used by *Pimentel et al.*[40,41] for the operation of the first chemical laser. The reaction of chlorine and hydrogen was initiated in this case in a quartz tube by flash photolysis (see Fig. 7).

$$\begin{aligned} Cl_2 + h\nu &\longrightarrow 2Cl \\ Cl + H_2 &\longrightarrow HCl + H \quad \text{(see Section 5)} \\ H + Cl_2 &\longrightarrow HCl^* + Cl \end{aligned} \qquad (3)$$

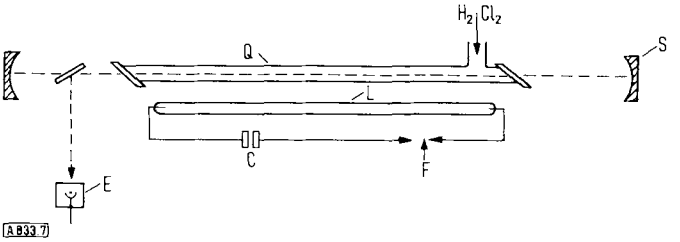


Fig. 7. Scheme of the HCl laser arrangement after *Pimentel et al.* [40]. Q: quartz tube ($d = 14$ mm, $l = 600$ mm) with NaCl windows fitted at the Brewster angle, L: xenon flash lamp, C: condenser ($E = 2000$ Ws), F: spark gap, S: concave mirror, E: InSb photocell.

Oblique NaCl windows fitted at the ends of the reaction tube allowed the IR emission of the HCl* molecule to emerge without loss. This emission was reflected back into the reaction tube by two laser mirrors; and beyond a certain intensity, it causes a concerted emission by the HCl* molecules formed in reaction (3).

2.3. Reaction with O_2 and NO

There are two possibilities for the reaction of hydrogen atoms with O_2. At low temperatures ($T < 500$ °K), addition of the H atom predominates in the presence of a third collision partner (M).

$$H(^2S) + O_2(^3\Sigma) \xrightarrow{+M} HO_2(^2A'); \quad \Delta H_0^0 = -47 \text{ kcal mole}^{-1} \qquad (6)$$
$$k_6 = 8 \times 10^{15} \text{ (M = Ar) cm}^6 \text{ mole}^{-2} \text{ s}^{-1} \text{ at } 298 \text{ °K [42, 43]}$$

In the hydrogen/oxygen explosion at the second explosion limit this reaction path competes with what is probably the most important reaction for combustion processes, *i.e.* the production of O atoms and OH radicals by

$$H(^2S) + O_2(^3\Sigma) \longrightarrow OH(^2\Pi) + O(^3P); \quad \Delta H_0^0 = 16.7 \text{ kcal mole}^{-1} \qquad (7)$$
$$k_7 = 2 \times 10^{14} \exp(-16.8/RT) \text{ cm}^3 \text{ mole}^{-1} \text{ s}^{-1} \text{ [*] [45, 46]}$$

Whereas reaction (7) proceeds very slowly at room temperature ($k_7 < 10^3$ cm^3 mole^{-1} s^{-1}) for H atoms in the ground state (^{2}S), H atoms in the first excited state (^{2}P) react very rapidly with O_2 to form electronically excited OH radicals[44].

$$\begin{aligned} H(^2P) + O_2(^3\Sigma) &\longrightarrow OH(^2\Sigma) + O(^3P) \\ OH(^2\Sigma) &\longrightarrow OH(^2\Pi) + h\nu \quad (\lambda \approx 3064 \text{ Å}) \end{aligned}$$

NO behaves in the same manner as O_2:

$$H(^2S) + NO(^2\Pi) \xrightarrow{+M} HNO^{\blacktriangle}(^1A''); \quad \Delta H_0^0 = -49 \text{ kcal mole}^{-1} \qquad (8)$$
$$k_8 = 8.7 \times 10^{15} \text{ (M = Ar) cm}^6 \text{ mole}^{-2} \text{ s}^{-1} \text{ at } 293 \text{ °K [47]}$$
(HNO$^{\blacktriangle}$ denotes an electronically excited HNO radical)

The initially formed HNO radical can rapidly react further with H atoms,

$$H + HNO \longrightarrow H_2 + NO; \quad \Delta H_0^0 = -55 \text{ kcal mole}^{-1} \qquad (9)$$
$$k_9 = 10^{11} \text{ cm}^3 \text{ mole}^{-1} \text{ s}^{-1} \text{ at } 298 \text{ °K [48]}$$

[*] The apparent activation energy (E_{exp}) is given here and in the following discussion in kcal mole^{-1}.

so that homogeneous recombination of the H atoms to form H_2 occurs. This property is also shown by nitric oxide in reactions with other atoms (O, halogens, *etc.*) and explains the important part played by NO as a free-radical scavenger in classical kinetics.

NO has recently also been used for the inexpensive quantitative detection of some types of atoms. In the case of H atoms this is achieved as follows: The electronically excited HNO molecule ($HNO^{\blacktriangle}$) formed in reaction (8) can reach the ground state by emission of light.

$$HNO^{\blacktriangle}(^1A'') \longrightarrow HNO(^1A') + h\nu \quad (\lambda \approx 7000\ \text{Å})$$

The intensity of the luminescence ($I_{HNO^{\blacktriangle}}$) is proportional to [H] and [NO], and can be determined quantitatively with a photomultiplier fitted with a suitable filter[49]. At a constant NO concentration, the luminescence can thus serve as a measure of the relative concentration of H atoms.

To determine the absolute concentration of H atoms, the HNO emission is used as an "indicator" for a "titration" of the H atoms in the gas phase. The H atoms are allowed to react *e.g.* with NOCl:

$$H + ClNO \longrightarrow HCl + NO;\ \Delta H_0^0 = -64\ \text{kcal mole}^{-1} \qquad (10)$$
$$k_{10} \geq 2 \times 10^{12}\ \text{cm}^3\ \text{mole}^{-1}\ \text{s}^{-1}\ \text{at}\ 298\,^\circ\text{K}\ [49]$$

This reaction results in the disappearance of H and the production of NO, which leads to HNO emission in accordance with the above scheme in the presence of H. When the quantity of NOCl added corresponds exactly to the original H concentration, the luminescence completely disappears, since all the H atoms have been consumed. The "end point" can therefore be accurately determined with a photomultiplier. As in a normal titration, one must naturally ensure that no interfering reactions occur.

Other titration and indicator reactions are listed in Table 1.

Table 1. Quantitative detection of atoms by titration in the gas phase.

Atom	Indicator reaction	Emission	Titration reaction	Ref.
H	$H+NO \rightarrow HNO^{\blacktriangle}$	$I_{HNO^*} \sim [H]\cdot[NO]$	$H+ClNO \rightarrow HCl+NO$	[49]
N	$N+N \rightarrow N_2^{\blacktriangle}$	$I_{N_2^*} \sim [N]^2$	$N+NO \rightarrow N_2+O$	[50]
O	$O+NO \rightarrow NO_2^{\blacktriangle}$	$I_{NO_2^*} \sim [O]\cdot[NO]$	$O+NO_2 \rightarrow NO+O_2$	[51]
Cl	$Cl+Cl \rightarrow Cl_2^{\blacktriangle}$	$I_{Cl_2^*} \sim [Cl]^2$	$Cl+ClNO \rightarrow Cl_2+NO$	[52]

2.4. Reactions with Hydrocarbons

Reactions of hydrogen atoms with hydrocarbons are important in the oxidation, pyrolysis, radiolysis, and photolysis of the latter. In the reaction of H atoms with hydrocarbons, the number of products and possible further reactions usually increases very markedly after only a few steps, so that a reliable determination of the primary steps was impossible for a long time. Recent results will be given here for some typical examples which allow an understanding of the reactions of H atoms with hydrocarbons making use of the known bond energies.

In the reaction of H atoms with paraffins, the first reaction step yields H_2 and the corresponding alkyl radical[*].

$$H + RH \longrightarrow H_2 + R^{\bullet}$$

Unsaturated hydrocarbons, as expected, exhibit a different reaction behavior. The first step in this case is addition of the H atom, which usually involves a much lower activation barrier than for the formation of H_2 in the first step (see Fig. 8).

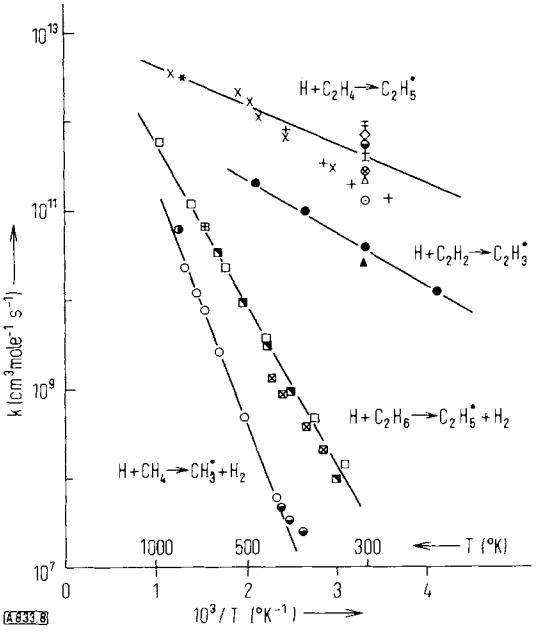


Fig. 8. Arrhenius diagram of experimental rate constants for the reactions of hydrogen atoms with simple hydrocarbons.
○ [66], ◑ [68], ◒ [67]; ⊠ [71], □ [69], ◪ [70], ⊞ [72]; ● [64], ▲ [65]; * [55], × [56], + [54], ⊙ [57], △ [58], ⊗ [60], ◊ [61–63], ⊕ [59].

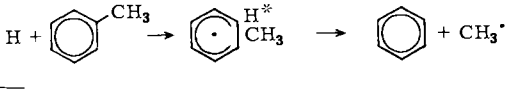
The addition of the H atom results initially in the formation of a highly vibrationally excited radical.

$$H + C_2H_2 \rightleftharpoons C_2H_3^{\bullet *} \qquad (11)$$
$$H + C_2H_4 \rightleftharpoons C_2H_5^{\bullet *} \qquad (12)$$
$$H + C_6H_6 \rightleftharpoons C_6H_7^{\bullet *} \qquad (13)$$

There are several possibilities for the further reaction of such radicals:

1. They may decompose back into the starting materials, as indicated in the above scheme.

2. Substitution may occur; for example, the reaction of H with toluene at 390 °K proceeds as follows



[*] Exchange reactions can also be detected with isotopes (*e.g.* tritium atoms with high kinetic energy) [53].

3. They may be deactivated by collisions to below the dissociation limit, and then react further.

Which of these possibilities predominates and determines the further course of the reaction depends on the external conditions (pressure, concentration of the reactants).

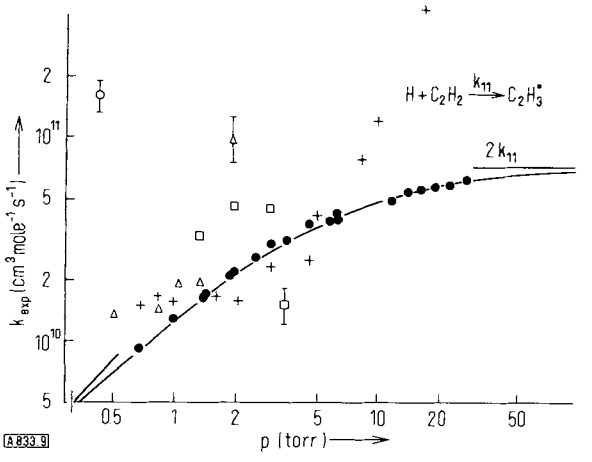


Fig. 9. Dependence of the experimental rate constants (k_{exp}) for the reaction $H + C_2H_2$ on the pressure ($T = 298\,°K$).
+ [77], △ [73], □ [65], ⊽ [78], ⊽ [79], ⊽ [76], ● [64].

The pressure dependence of the rate constant for the homogeneous reaction of acetylene with H atoms is as shown in Fig. 9. Under the conditions indicated, no C_2H_2 is consumed, and the H atoms appear as H_2. Their concentration decreases in accordance with

$$\frac{d[H]}{dt} = -k_{exp}[C_2H_2][H]$$

with the aid of isotopic studies, the following mechanism could be established:

$$H + C_2H_2 \rightleftharpoons C_2H_3^{\bullet *} \quad (11a)$$
$$k_{11} = 3.5 \times 10^{10}\,cm^3\,mole^{-1}\,s^{-1} \text{ at } 298\,°K$$
$$C_2H_3^{\bullet *} + M \longrightarrow C_2H_3^\bullet + M \quad (11b)$$
$$C_2H_3^\bullet + H \longrightarrow (C_2H_4)^* \longrightarrow C_2H_2 + H_2 \quad (11c)$$

At pressures above 50 torr (see Fig. 9), most of the vibrationally excited vinyl radicals (excitation energy $E^* \approx 39$ kcal mole^{-1}) are deactivated to below the dissociation limit, and react further with H[*], so that the reaction course is determined only by the first step (k_{11}). If the reaction is allowed to take place with D atoms instead of H atoms, the main reaction at $p < 1$ torr is substitution (case 2):

$$D + C_2H_2 \longrightarrow C_2H_2D^{\bullet *} \longrightarrow C_2HD + H; \quad (11a')$$
$$\Delta H_0^\circ = -1.6\,kcal\,mole^{-1}$$
$$k_{11} = 10^{13}\exp(-3.60/RT)\,cm^3\,mole^{-1}\,s^{-1}\,[74]$$

The lifetime of $C_2H_2D^{\bullet *}$ for the exothermic removal of a H atom (difference between the C—H and C—D zero-point energies) is much shorter than for the regeneration of D.

[*] The vibrationally excited ethylene $(C_2H_4)^*$ in reaction (11c), on the other hand, decomposes further almost immediately; much higher pressures are required to stabilize this species.

In the reaction of H atoms with an alkene (ethylene in this case), the first two steps are as in the case of acetylene[60]

$$H + C_2H_4 \rightleftharpoons C_2H_5^{\bullet *} \quad (12)$$
$$k_{12} = 8 \times 10^{11}\,cm^3\,mole^{-1}\,s^{-1} \text{ at } 298\,°K$$
$$C_2H_5^{\bullet *} + M \longrightarrow C_2H_5^\bullet + M$$

In the next step of the reaction[*], in contrast with the fate of the vinyl radical, the C—C bond is broken[75].

$$C_2H_5^\bullet + H \longrightarrow C_2H_6^* \longrightarrow 2CH_3^\bullet \quad (14)$$
$$k_{14} \approx 4 \times 10^{13}\,cm^3\,mole^{-1}\,s^{-1} \text{ at } 298\,°K\,[60]$$

Various modern methods have been used to measure the rate constant of reaction (12). It is only recently, however, that correct allowance appears to have been made for the pressure dependence of the secondary reactions which cause the pronounced scatter of the experimental results[61, 63].

If the value of k_{12} for ethylene is known, the absolute values for the addition of H atoms to other olefins can be found from the ratios of the rate constants, which can be determined photochemically (see Table 2).

Table 2. Relative rate constants (based on ethylene) for the addition of hydrogen atoms to olefins at room temperature [80].

Olefin	$k_{Olefin}/k_{C_2H_4}$
Ethylene	≡1.00
Propene	1.53
1-Butene	1.58
Isobutene	3.85
2-*cis*-Butene	0.72
2-*trans*-Butene	0.90
1,3-Butadiene	7.5
1-Pentene	1.36
Trimethylethylene	1.57
2-*cis*-Pentene	0.60
2-*trans*-Pentene	0.67
Tetramethylethylene	1.28

Even more reaction paths are possible in the reaction of H atoms with benzene.

$$H + C_6H_6 \longrightarrow C_6H_7^{\bullet *} \quad (13)$$
$$k_{13} = 10^{13}\exp(-3.8/RT)\,cm^3\,mole^{-1}\,s^{-1}$$

Cyclohexadienyl radicals are formed in the first step[81]. Further reaction with H atoms can then lead both to H_2 and various cyclic C_6 hydrocarbons (cyclohexane, cyclohexene, cyclohexadiene) and, with ring cleavage, to the corresponding acyclic C_6 hydrocarbons[82, 83].

The examples mentioned show that the further course of the reactions of hydrogen atoms with hydrocarbons is strongly dependent on the behavior of the initially formed excited radicals. If the bond energies are known, the theory of unimolecular reactions[84] is a useful tool for the determination of the probabilities of the various reaction paths under the prevailing conditions (pressure, temperature). At high temperatures ($T > 1000\,°K$), it must also be noted that addition and abstraction can compete with each other.

[*] The reaction (14) is also the first subsequent step in the reaction of H atoms with ethane ($H + C_2H_6 \rightarrow C_2H_5^\bullet + H_2$).

3. Carbon Atoms

Reactions of free carbon atoms have been subjected to several qualitative studies, but the measurement of reaction rates is still in its early stages[85–87].

A serious difficulty in the investigation of the reactions of C atoms is their production. *Wolfgang et al.*[85] obtained readily detectable radioactive ^{11}C atoms by the nuclear process $^{12}C(\gamma,n)\rightarrow{}^{11}C$, and these were thermalized by the addition of an inert gas (Ne). *Skell* and *Engel*[86] used C atoms from a carbon arc burning under vacuum, the reactants being condensed on the walls of the vacuum container at 77 °K. These methods have allowed conclusions to be drawn regarding reaction mechanisms. The main final products in the reactions of ^{11}C atoms with hydrocarbons were acetylene and ethylene, whereas the second method led mainly to higher hydrocarbons, which were formed by "insertion" of the C atom into bonds of the substrate molecule.

Two other methods have so far been used for the determination of rate constants. *Wolf et al.*[88] produced ^{14}C atoms by dissociation of $^{14}C_3O_2$ in a microwave discharge. *Braun et al.*[89] have detected carbon atoms in the ground state $C(^3P)$ and in the excited states $C(^1D)$ ($E^*=30$ kcal mole^{-1}) and $C(^1S)$ ($E^*=62$ kcal mole^{-1}) by their absorption in the vacuum UV after flash photolysis of C_3O_2. Table 3 shows a comparison of the rate constants for reactions of C atoms in various electronic states.

Table 3. Rate constants for reactions of carbon atoms in various electronic states [88—91].

Reaction	k (298 °K) (cm^3 mole^{-1} s^{-1}) $C(^3P)$	$C(^1D)$	$C(^1S)$
$C(X)+H_2(^1\Sigma)\rightarrow CH+H$	$<10^6$	2.5×10^{13}	2.3×10^{12}
$C(X)+O_2(^3\Sigma)\rightarrow CO+O$	2×10^{13}	3×10^{12}	—
$C(X)+NO(^2\Pi)\rightarrow CN+O$	6.6×10^{13}	6×10^{13}	—
$C(X)+CH_4(^1A_1)\rightarrow C_2H_2+H_2$	$<10^8$	1.9×10^{13}	—

The results for the reaction with H_2 can be clearly illustrated by the correlation diagram reproduced in Figure 10[92]. Reaction to form $CH(^2\Pi)$ and $H(^2S)$ is endothermic for $C(^3P)$ atoms ($\Delta H_0^0=+20$ kcal mole^{-1}), and is therefore very slow at room temperature[93]. For $C(^1D)$, the formation of $CH(^2\Pi)$ and $H(^2S)$ is exothermic, and proceeds rapidly, whereas the reaction of $C(^1S)$, which is more exothermic by more than 30 kcal mole^{-1}, is at least one order of magnitude slower. This example shows that energy and spin considerations ($C(^1D)$ and $C(^1S)$ have the same spin state, and the reaction with $H_2(^1\Sigma)$ to form $CH(^2\Pi)$ and $H(^2S)$ is "spin-allowed") are often insufficient by themselves for the prediction of the rate of an elementary reaction. However, the result can be explained on the basis of symmetry considerations, according to which there is no "continuous" (adiabatic) potential-energy surface for the analogous reaction of the $C(^1S)$ atoms (see Fig. 10).

Only ten gas-kinetic collisions are necessary for the reaction of a molecule of O_2 with $C(^3P)$ atoms to form CO and O. Formation of CO_2 by "insertion" of $C(^3P)$ has been observed neither at high pressures nor in the liquid phase. It is therefore assumed that the attack of the C atom takes place at the end of the O_2 molecule, and not on the π bond[85].

$C(^3P)$ atoms surprisingly react relatively slowly with hydrocarbons at room temperature. The rate constants for

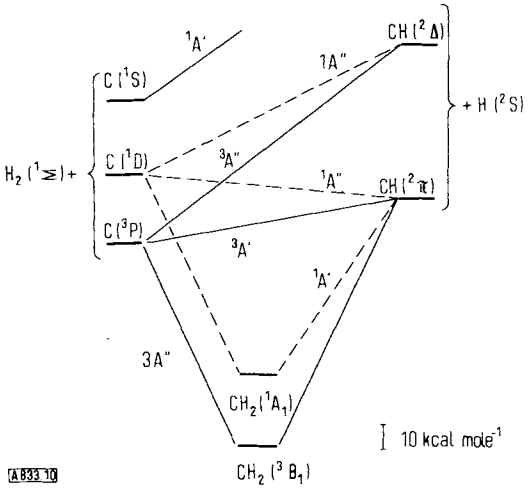


Fig. 10. Correlation diagram for the reactions of H_2 with carbon atoms in various electronic states [92].

the reactions with CH_4, C_2H_2, and C_2H_4 are less than 10^7 cm^3 mole^{-1} s^{-1}[88]. The corresponding reactions of $C(^1D)$ are fast; the reaction with CH_4 leads directly to the formation of C_2H_2 (see Table 3).

4. Oxygen Atoms

Reactions of free oxygen atoms determine the course of many oxidation and combustion processes[94]. As biradicals, they exhibit a great diversity of possible reactions, and the primary products of many of their reactions have only recently been definitely established by direct investigations.

4.1. Generation of $O(^3P)$ and $O(^1D)$ Atoms

If O atoms are generated by an electric discharge in molecular oxygen,

$$O_2(^3\Sigma) \xrightarrow{\text{electric discharge}} O(^3P)$$
$$O_2(^1\Delta_g);\ E^* = 22.5 \text{ kcal mole}^{-1}$$
$$O_2(^1\Sigma_g);\ E^* = 37.5 \text{ kcal mole}^{-1}$$
$$O + O_2 \xrightarrow{+M} O_3$$

metastable oxygen molecules in electronically excited states are obtained as well as O atoms in the ground state $O(^3P)$; these metastable molecules are very insensitive to wall collisions, and can therefore lead to interfering parallel reactions, though not to the same degree as in the case of N_2[95,96]. Ozone is also formed in the presence of O_2.

$O(^3P)$ atoms can also be produced in the absence of O_2 in the "titration reaction" mentioned earlier (cf. Table 1),

$$N(^4S) + NO(^2\Pi) \longrightarrow N_2(^1\Sigma) + O(^3P)$$

in the Hg-sensitized photolysis of N_2O

$$N_2O(^1\Sigma) + Hg(^3P_1) \longrightarrow O(^3P) + N_2(^1\Sigma) + Hg(^1S_0)$$

or on vacuum UV photolysis of NO[97].

$$NO(^2\Pi) + h\nu\ (\lambda < 1915\,Å) \longrightarrow N(^4S) + O(^3P)$$

O atoms can be produced in the first electronically excited state ($O(^1D)$; $E^* = 45$ kcal mole^{-1}) by photolysis of ozone,

$$O_3 + h\nu\ (\lambda < 3100\,Å) \longrightarrow O_2(^1\Delta_g) + O(^1D)$$

$N_2O(\lambda < 2200$ Å), or $O_2(\lambda < 1760$ Å). Their radiation lifetime is very long ($\tau \approx 110$ s), but they can be rapidly deactivated by O_2, N_2, *etc.*[98].

4.2. Reaction with H_2

The reaction of atomic oxygen with H_2

$$O(^3P) + H_2(^1\Sigma) \longrightarrow OH(^2\Pi) + H(^2S);\ \Delta H_0^0 = 1.9\ \text{kcal mole}^{-1} \quad (15)$$

is important as a chain-branching step in the oxygen/hydrogen reaction and numerous other oxidation reactions. Apparent activation energies of between 6 and 12 kcal mole^{-1} were reported for this reaction a few years ago[99, 100]. Figure 11 shows that the rate constants determined by modern methods (shock waves, explosion limits, stirred reactor, flow system) can be represented very well over a wide temperature range (320—2500 °K) by an Arrhenius expression

$$k_{15} = 1.5 \times 10^{13} \exp(-9.4/RT)\ \text{cm}^3\ \text{mol}^{-1}\ \text{s}^{-1}$$

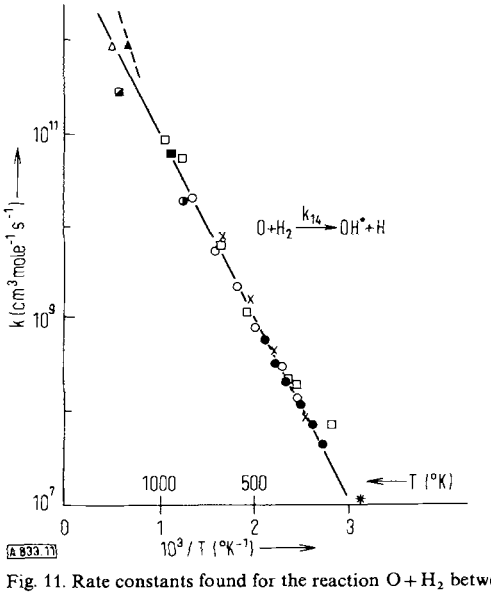


Fig. 11. Rate constants found for the reaction $O + H_2$ between 320 and 2500 °K.
○ [106], □ [107], ● [108], × [104], * [109], ◑ [105], ■ [103], ◪ [110], -△- [101], --▲-- [102].

4.3. Reactions with Alkanes

As in the reaction with H_2, an H atom is apparently also transferred from saturated hydrocarbons to the attacking $O(^3P)$ atom,

$$O(^3P) + RH \longrightarrow R^\bullet + OH^\bullet$$

Table 4. Rate constants for reactions of $O(^3P)$ atoms with alkanes [111, 112].

$O(^3P) + RH \rightarrow R^\bullet + OH^\bullet$	A-Factor (cm^3 mole^{-1} s^{-1})	E_{exp} (kcal mole^{-1})
$O(^3P) + CH_4 \rightarrow CH_3^\bullet + OH^\bullet$	$10^{13.3}$	9.2
$O(^3P) + C_2H_6 \rightarrow C_2H_5^\bullet + OH^\bullet$	$10^{13.4}$	6.1
$O(^3P) + n\text{-}C_4H_{10} \rightarrow i\text{-}C_4H_9^\bullet + OH^\bullet$	$10^{13.8}$	5.1
$O(^3P) + n\text{-}C_7H_{16} \rightarrow i\text{-}C_7H_{15}^\bullet + OH^\bullet$	$10^{14.0}$	4.3

the measured activation energies (E_{exp}) decreasing with decreasing H—R bond strength (see Table 4). The rate of the overall consumption of O atoms increases in proportion to the nature and number of the C—H bonds in the case of higher paraffins. For the attack of O atoms on primary, secondary, and tertiary C—H bonds of the alkanes, many of the experimental results can be described by the following Arrhenius expressions (per C—H bond)[112]

$$k_{primary} = 5 \times 10^{12} \exp(-5.8/RT)\ \text{cm}^3\ \text{mole}^{-1}\ \text{s}^{-1}$$
$$k_{secondary} = 1.3 \times 10^{13} \exp(-4.5/RT)\ \text{cm}^3\ \text{mole}^{-1}\ \text{s}^{-1}$$
$$k_{tertiary} = 1.6 \times 10^{13} \exp(-3.3/RT)\ \text{cm}^3\ \text{mole}^{-1}\ \text{s}^{-1}$$

Attack by $O(^1D)$ atoms, on the other hand, takes place without an activation barrier with insertion of $O(^1D)$ into the CH bond.

$$O(^1D) + RH \longrightarrow ROH^*$$

The resulting alcohol molecule exhibits strong vibrational excitation, and can be stabilized only at high pressures or in the liquid phase (see Table 5).

Table 5. Reactions of excited oxygen atoms with alkanes.

$O(^1D) + RH \rightarrow ROH^*$				Conditions	Re
$O(^1D) + CH_4$	$\xrightarrow{+M}$	CH_3OH^*	(70%)	87 °K, liquid Ar	[11
	$\longrightarrow$	$CH_3^\bullet + OH^\bullet$	(30%)		
$O(^1D) + C_2H_6$	$\xrightarrow{+M}$	$C_2H_5OH^*$	(97%)	87 °K, liquid Ar	[11
	$\longrightarrow$	$C_2H_4 + H_2O$	(3%)		
$O(^1D) + i\text{-}C_4H_8$	$\xrightarrow{+M}$	$i\text{-}C_4H_7OH^*$	(90%)	300 °K, 1200 torr N_2	[11
	$\xrightarrow{+M}$	$t\text{-}C_4H_7OH^*$	(10%)		

4.4. Reaction of $O(^3P)$ Atoms with Acetylene

The most important of the elementary steps occurring in the reaction of $O(^3P)$ with C_2H_2 are indicated, together with their rate constants, in Figure 12.

An addition complex $(C_2H_2O)^*$ is first formed. The experimental activation energy ($E_{exp} = 3.0$ kcal mole^{-1}; see Fig. 13) required for this step agrees well with the value

obtained in the addition of H atoms (see Section 2.4) to C_2H_2. However, whereas the excited $C_2H_3^*$ radicals can decompose only in a reversal of their formation reaction, several decomposition paths are conceivable for the $(C_2H_2O)^*$ complex.

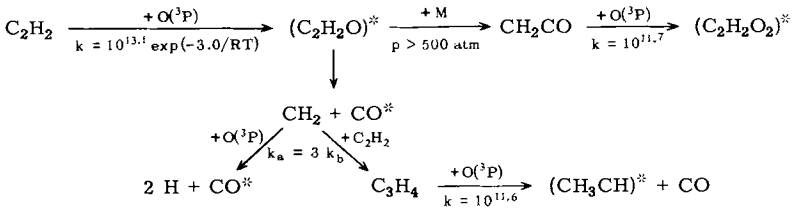
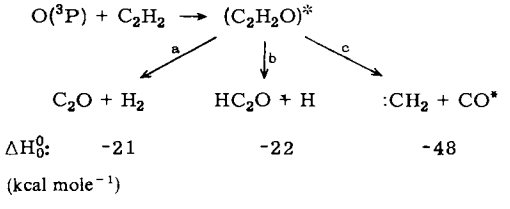


Fig. 12. Elementary steps in the reaction of oxygen atoms with acetylene. Rate constants at $T=298\,°K$, in $cm^3\ mole^{-1}\ s^{-1}$.



The most exothermic decomposition (c) into $:CH_2$ and CO* predominates. The two hydrogen atoms formed on further reaction of the methylene with $O(^3P)$ atoms can be detected quantitatively with an ESR spectrometer (see Fig. 2)[117]. Strong vibrational excitation ($v \leqslant 13$) is found for the CO*[121].

In an excess of C_2H_2, the carbene reacts with acetylene to form C_3H_4, which is present mainly as methylacetylene and allene. Stabilization of the $(C_2H_2O)^*$ complex to

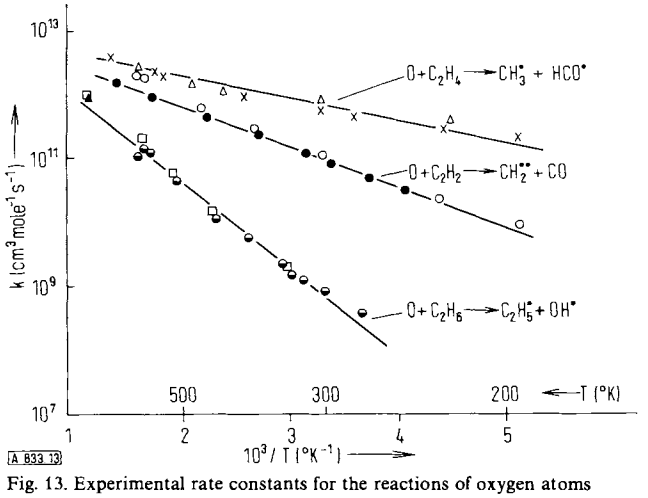


Fig. 13. Experimental rate constants for the reactions of oxygen atoms with C_2 hydrocarbons.
△ [120], × [119], ● [117], ○ [118], □ [111], ⬬ [107], ▲ [116].

ketene occurs only at very high pressures ($p > 500$ atm) or in an argon matrix[122] (20 °K).

In addition to the reactions shown in Figure 12, the decomposition paths (a) and (b), and reactions that lead to the formation of free electrons and ions and to chemiluminescence of CO, OH, CH, and C_2 also occur to a small extent[123–125].

4.5. Reactions with Olefins

The reactions of oxygen atoms with olefins are very similar to the corresponding reactions of the CH_2 radical, which is isoelectronic with O[126, 127].

The addition of $O(^3P)$ atoms is not stereospecific. According to *Cvetanovic*[126], this addition first yields triplet biradicals, whose lifetime is comparable with the period of rotation about the C—C bond, and which isomerize by ring closure and migration of H atoms or alkyl groups to form epoxides, aldehydes, and ketones. On the basis of studies on the addition of $O(^3P)$ atoms to condensed olefins (90 °K), *Scheer et al.*[128] conclude that the isomerization and the localization of the O atom must take place simultaneously. Information on this point should be provided in the future by measurements on the rate constants of reactions of $O(^3P)$ atoms with the corresponding deuterated compounds.

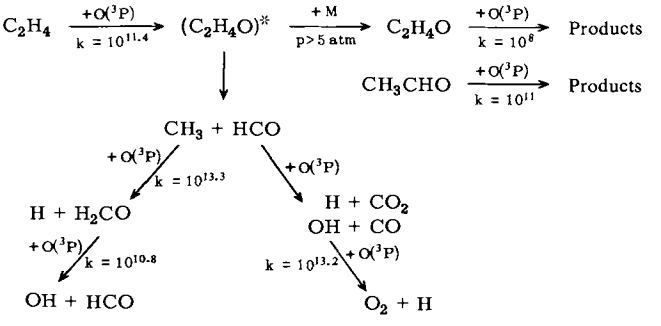


Fig. 14. Elementary steps in the reaction of oxygen atoms with ethylene. Rate constants at $T=298\,°K$, in $cm^3\ mole^{-1}\ s^{-1}$.

Figure 14 shows the elementary steps occurring in the reaction of $O(^3P)$ atoms with ethylene. As in the reaction of H atoms (see Fig. 8), the energy barrier to be overcome is lower than in the case of acetylene (see Fig. 13). Stabilization of the $(C_2H_4O)^*$ complex to form ethylene oxide and acetaldehyde takes place to a considerable extent even at atmospheric pressure. These compounds react further relatively slowly with $O(^3P)$, and can therefore be readily detected as end products and used for the determination

Table 6. Relative rate constants at $T=298\,°K$ for the addition of oxygen, sulfur, and selenium atoms to olefins [129—132].

Olefin	$O(2^3P)$	$S(3^3P)$	$Se(4^3P)$
$H_2C{=}CH_2$	≡ 1	≡ 1	≡ 1
$H_2C{=}CH{-}CH_3$	5.8	7.8	2.6
$H_2C{=}CH{-}CF_3$	0.06	—	—
$H_2C{=}CH{-}C_2H_5$	5.8	11	7.1
$H_2C{=}C(CH_3)_2$	23	56	44.7
$H_2C{=}C(CH_3)CF_3$	0.5	—	—

of relative rate constants. Table 6 gives relative rate constants for some olefins. These values clearly show an electrophilic character of the $O(^3P)$ addition to olefins, which is also evident in the analogous reactions of $S(3^3P)$ and $Se(4^3P)$ atoms.

4.6. Reactions with Sulfur Compounds

During the oxidation of simple sulfur compounds (H_2S, CS_2, COS, S_2), the presence of O atoms can be seen from an intense blue-violet SO_2 chemiluminescence, which was assigned to the recombination of SO with O as early as 1934 by *Gaydon*[133]. However, a definite identification of the elementary steps and the determination of their rate constants became possible only through the isolated investigation of these reactions in a flow system coupled with a mass spectrometer. The mass-spectrometric detection, unlike other spectroscopic methods, is not tied to special properties of the particles to be detected, so that it is possible, in principle, to detect quantitatively all the stable and unstable starting materials, intermediates, and end products of a reaction with high sensitivity. The problem here is the correct "handling" of the unstable particles, which must pass into the ion source as directly as possible, *i.e.* without collisions with the vessel walls.

Most arrangements for the combination of a mass spectrometer with a flow reactor are based on a principle first described by *Eltenton*[134] (see Fig. 15a). A short distance from the end of the flow tube is a plate with an aperture

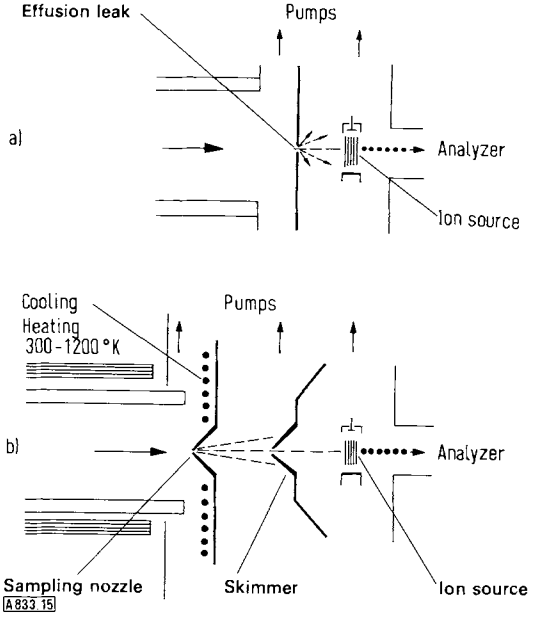


Fig. 15. Sampling for the analysis of unstable particles with the mass spectrometer.

a) Effusion arrangement after [134]; b) molecular beam inlet after [136—138].

10—100 μm wide (corresponding to the mean free path in the tube), through which the gas can diffuse directly into the ion source. Atoms and radicals can indeed be detected in this way, but particles pass into the ion source from a region in which the influence of the wall and of the flow boundary layer is clearly noticeable. For unstable particles, this can cause marked differences in concentration compared to that in the actual reaction. These disadvantages are avoided if the gas samples are taken with a conical probe that is adjusted to the flow[135] and whose aperture is large in relation to the mean free path in the flow tube (see Fig. 15b)[136—138].

The reaction tube is thermally insulated and placed inside a vacuum-tight stainless steel jacket, and can be electrically heated. The sampling probe (quartz cone) is attached to an intermediate vacuum chamber, which is evacuated with a diffusion pump, so that a pressure of between 10^{-3} and 10^{-4} torr is produced with a pressure of 1—20 torr in the flow system and a probe aperture of 1 mm. The gas samples are taken from a region several mm in diameter in front of the tip of the probe, so that only a very small percentage of the entering particles can come into contact with the wall. The density and translational temperature decrease by several orders of magnitude within a few microseconds in the freely expanding jet, and this corresponds to ideal "quenching" of the drawn off sample. The jet impinges on a cone of stainless steel, the "skimmer", which outs out the outer part of the jet. The apex angle of the cone is so chosen that the particles inside the cone do not undergo collisions with the wall of the cone, and the particles reflected from

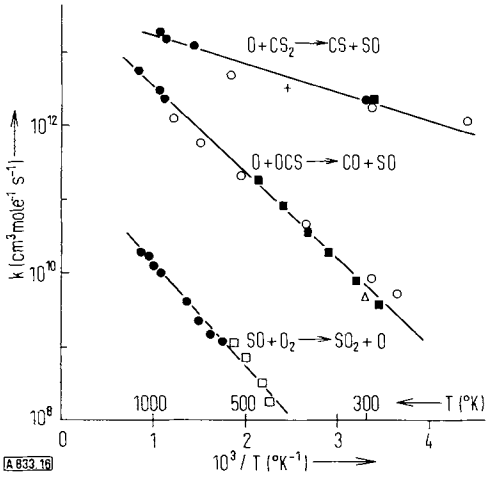


Fig. 16. Experimental rate constants for elementary steps in the oxidation of carbon disulfide and carbonyl sulfide.

● [137, 138], ■ [136], ○ [58], △ [140], + [143], □ [141].

the outer wall do not pass downstream again. With the optimum distance between the aperture of the probe and the skimmer (in this case ≈10 mm), a sharply focused beam of high density enters the ion source.

Figure 16 shows the results (solid points are measurements using the entry system shown in Fig. 15b) for some particularly important elementary steps in the oxidation of CS_2 and of COS, in the form of an Arrhenius diagram. Though the reaction paths followed in the reaction of $O(^3P)$ atoms with CS_2 and with COS are analogous, a higher activation energy is found for the more exothermic reaction with COS. The rate constants found at room temperature for the reactions of $O(^3P)$ atoms with simple sulfur compounds are listed in Table 7.

Vibrational excitation of the product molecules (CO*, SO*, CS*) has been detected in some reactions. These are therefore promising candidates for a chemical laser. The elementary steps that lead to the formation of SO_2 are particularly interesting in connection with the problems of air pollution.

Table 7. Rate constants for reactions of $O(^3P)$ atoms with simple sulfur compounds at room temperature [136 to 148].

Reaction		log k ($cm^3\ mole^{-1}\ s^{-1}$)	$-\Delta H_0^\circ$ (kcal $mole^{-1}$)
$O(^3P)+CS_2(^1\Sigma)$	$\longrightarrow CS^*(^1\Sigma)+SO^*(^3\Sigma)$	12.3	32
	$\longrightarrow OCS(^1\Sigma)+S(^3P)$	< 8	53
$O(^3P)+OCS(^1\Sigma)$	$\longrightarrow SO(^3\Sigma)+CO^*(^1\Sigma)$	9.8	55
	$\longrightarrow CO_2(^1\Sigma)+S(^3P)$	< 7	57
$O(^3P)+SO_3(^3\Sigma)$	$\longrightarrow SO_2(^1A_1)+O_2(^3\Sigma)$	5.6	35
$O(^3P)+H_2S(^1A_1)$	$\longrightarrow OH(^2\Pi)+SH(^2\Pi)$	10.3	14
$O(^3P)+CS(^1\Sigma)$	$\longrightarrow CO^*(^1\Sigma)+S(^3P)$	>13	75
		($cm^6\ mole^{-2}\ s^{-1}$)	
$O(^3P)+SO(^3\Sigma)$	$\xrightarrow{+M} SO_2(^1A_1)$	17.5	130
$O(^3P)+SO_2(^1A_1)$	$\xrightarrow{+M} SO_3(^3\Sigma)$	15.0	83

4.7. Reaction with Ammonia and Hydrazine

At room temperature, ammonia is attacked only slowly by O atoms, as is also the case with H and N atoms. The rate constants plotted in Figure 17 were found in the temperature range from 300—900 °K for the probable primary step

$$O(^3P) + NH_3(^1A_1) \longrightarrow NH_2(^2B_1) + OH(^2\Pi); \quad (16)$$
$$\Delta H_0^\circ = +0.7\ \text{kcal mole}^{-1}$$

The further reaction is relatively complicated. In the absence of O_2, three O atoms are consumed per molecule of NH_3; H atoms, NO, H_2O, and O_2 are formed in a ratio of 1.6:1:0.7:0.6. HNO radicals have been detected as intermediates.

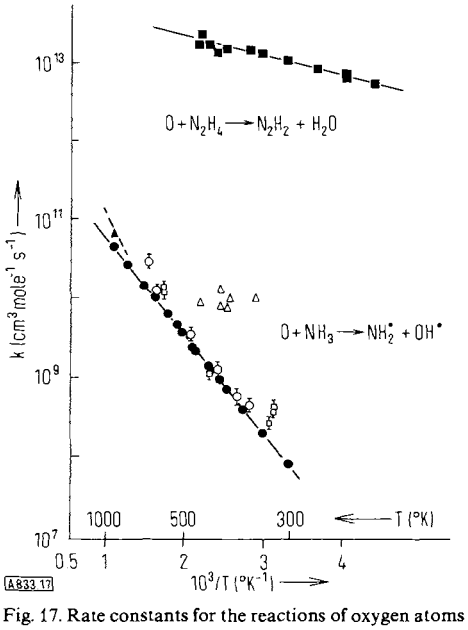


Fig. 17. Rate constants for the reactions of oxygen atoms with ammonia and hydrazine.
△ [149], --▲-- [150], ⊕ [151], ⊖ [153], ● [152], ■ [154].

As can be seen from Figure 17, hydrazine reacts extremely rapidly with atomic oxygen even at low temperatures. The overall reaction corresponds to

$$N_2H_4 + 4.5\,O \longrightarrow 2H + H_2O + 1.4\,O_2 + 0.6\,N_2 + 0.6\,NO + 0.1\,N_2O$$

The products formed in the primary step in this reaction have been detected directly with an arrangement (see Fig. 18) in which the sampling system shown in Figure 15b had been modified in such a way that the beam of O atoms from the flow system was made to react with a free beam of hydrazine in the intermediate vacuum chamber. It was found that the reaction leads *directly* to diimine and water.

$$O(^3P) + N_2H_4 \longrightarrow N_2H_2 + H_2O;\ \Delta H_0^{298} = -81\ \text{kcal mole}^{-1} \quad (17)$$

This reaction thus provided the first direct evidence that $O(^3P)$ atoms can take up two H atoms in one step[154, 155].

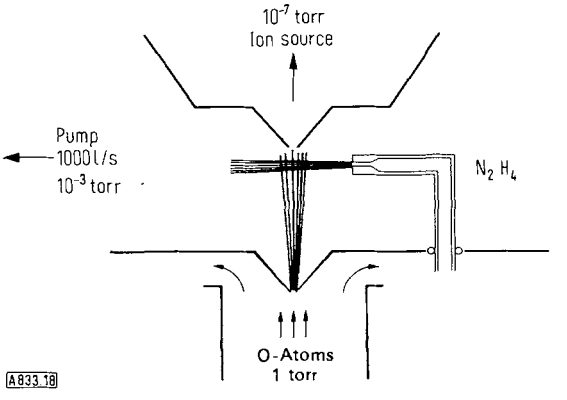


Fig. 18. Scheme of an arrangement for the direct determination of the primary products of elementary steps with crossed free jets [154].

5. Halogen Atoms

5.1. Reaction with H_2

Investigations on the reactions of halogens with hydrogen have played an important part in the development of reaction kinetics, starting with the classic experimental

studies of *Bodenstein*. *Nernst*'s observation that the photochemical chlorine/hydrogen reaction can be explained by the participation of chlorine atoms, as well as the mechanism proposed by *Christiansen*, *Herzfeld*, and *Polanyi* for the thermal reaction of hydrogen and bromine with allowance for the reactions of H and Br atoms, which explained the results of *Bodenstein*'s measurements, have not only established the participation of free atoms in gas phase reactions, but have also made a decisive contribution to our understanding of composite reactions (open reaction sequence, closed sequence, chain reaction).

Halogen atoms can be produced from the molecules either photochemically or thermally at easily accessible wavelengths and temperatures. Much information has therefore been available for a long time concerning the reactions of chlorine, bromine, and iodine atoms with H_2 (see Fig. 19) and other reactants[156].

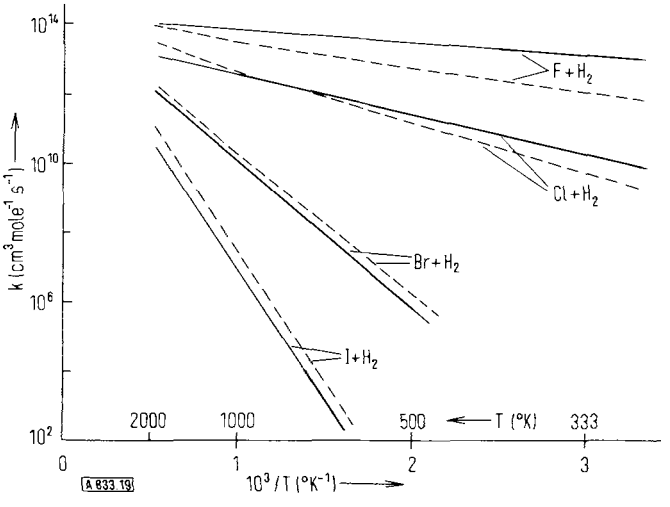


Fig. 19. Rate constants for the reactions of halogen atoms with hydrogen.
——— Experimental values [156, 165—168]; - - - Calculated values [162, 164].

A quantitative investigation of the reaction

$$F + H_2 \longrightarrow HF^* + H;\ \Delta H_0^0 = -32\ \text{kcal mole}^{-1} \qquad (18)$$

has only recently become possible. It was necessary to be able to produce F atoms in the absence of F_2, so that the reaction (18) could be observed without interference by the subsequent step $H + F_2$ (see Section 2.2). F atoms can be produced in the flow system at a low F_2 partial pressure ($[F] \approx 0.1$ torr, $[F_2] \approx 10^{-3}$ torr) by the reaction

$$N + NF_2 \longrightarrow N_2 + 2F$$

and used for the study of reaction (18)[157].

For flash photolysis, the condition mentioned is satisfied by the process

$$UF_6 + h\nu \longrightarrow F + UF_5$$

Pimentel and *Kompa*[158] isolated reaction (18) in a UF_6/H_2 mixture in this way. It can be shown by the pulsed HF laser emission that occurs at $\lambda = 2.7$—2.9 μm that HF* molecules are preferentially formed in the second vibration state ($N_v = 2/N_{v=1} = 3.5 - 5.5$) in reaction (18)[159].

A continuous HF laser emission with a power of 475 W was obtained by *Jacobs*, *Gross*, *et al.*[160] with an arrangement in which F atoms are produced by thermal dissociation of SF_6 (0.03 mole s^{-1}) and mixed with H_2 in an ultrasonic flow. It was possible in this way to obtain 12% of the energy liberated in the reaction (18) as radiation energy.

Cool, *Shirley*, and *Stephens*[161] produced F atoms by the reaction

$$NO + F_2 \longrightarrow FNO + F$$

and allowed them to react with D_2 in a flow apparatus to form DF*. On addition of CO_2, the excitation energy of the deuterium fluoride can be transferred to carbon dioxide (see Fig. 20).

$$DF^*_{(v=1)} + CO_{2(00^00)} \longrightarrow DF_{(v=0)} + CO^*_{2(00^01)}$$

This provided the first true "chemical" laser that does not need any additional energy sources (electric discharge, light flashes, *etc.*). An efficiency of 4.6% and a continuous beam power of 162 W at 10.6 μm have so far been achieved.

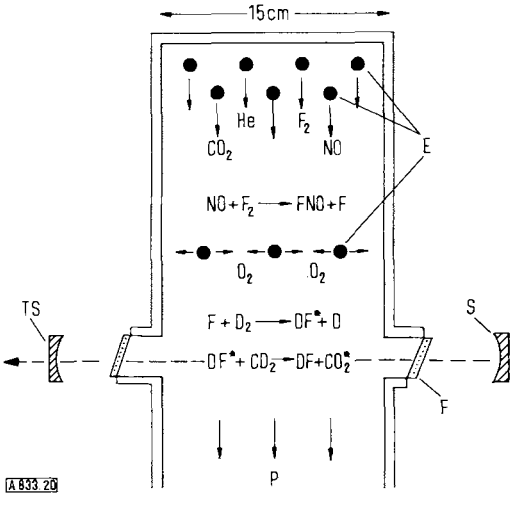


Fig. 20. Continuously operating "purely chemical" laser with a beam power of 162 W [161]. E: injectors, F: NaCl window, S: spherical mirror, TS: partially transmitting mirror, P: pump.

In addition to the experimental rate constants for the reactions of the halogen atoms with H_2, Figure 19 also shows the results of calculations by an empirical method described by *Johnston et al.*[162, 164]. This method (bond energy-bond order method) uses a simple valence model for reactions in which a H atom is transferred. It can be described for the reaction

$$\underset{(a)\ (b)}{H\uparrow\downarrow H} + \uparrow Cl \longrightarrow \underset{(a)\ (b)}{H\uparrow^{n_1}\cdots\downarrow H^{n_2}\uparrow Cl} \longrightarrow \underset{(a)\ (b)}{H\uparrow} + \underset{(a)\ (b)}{H\downarrow\uparrow Cl}$$

The reaction is considered in a linear arrangement. The electron of the transferred H atom (b) is assumed to have a spin orientation that allows a bond of order n_1 with the

second H atom (a) and of order n_2 with the Cl atom. Antibonding occurs between the Cl atom and the remaining H atom (a). Before the reaction, $n_1=1$ and $n_2=0$, while after the reaction, $n_1=0$ and $n_2=1$. During the reaction, n_1+n_2 should always be equal to 1, *i. e.* maximum bonding should always prevail. With the aid of the empirical relations between bond order (n) and bond energy (E) given by *Pauling*[163], this model allows a relatively simple calculation of the potential energy of the system along the reaction path.

Though this method does not give the entire potential-energy surface for the reaction, the information required for a calculation of the rate constants according to the transition state theory (height of the potential-energy barrier, properties of the activated complex) can be obtained.

Surprisingly good agreement with the experimental values is often obtained when one considers the small amount of calculation and the simple model used.

5.2. Reactions with Hydrocarbons

In the determination of the rate constants of the reactions of halogen atoms with hydrocarbons, the reaction with H_2 is usually used as a reference reaction.

Table 8 gives some examples of reactions of the type

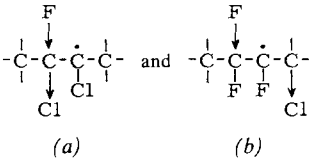
$$RH + F \longrightarrow R^{\bullet} + HF$$

Table 8. Rate constants for reactions of F atoms with hydrocarbons [168].

Reaction	log A (per H-Atom) ($cm^3\ mole^{-1}\ s^{-1}$)	E_{exp} ($cal\ mole^{-1}$)
$F(^2P_{3/2})+CH_3Cl$	13.5	1010
CH_2Cl_2	12.8	100
$CHCl_3$	12.9	600
$CHCl_2F$	13.5	1280
$CHClF_2$	13.1	1260
Primary CH bonds		
$F(^2P_{3/2})+CH_4$	14.5	1150
C_2H_6	13.4	220
C_3H_8	13.2	−60
n-C_4H_{10}	13.1	−60
iso-C_4H_{10}	13.1	−60
neo-C_5H_{12}	13.1	−60
Secondary CH bonds		
$F(^2P_{3/2})+$ *cyclo*-C_3H_6	13.2	−60
C_3H_8	13.2	−60
n-C_4H_{10}	13.1	−60
Tertiary CH bonds		
$F(^2P_{3/2})+$ *iso*-C_4H_{10}	13.3	−60

The data show that from ethane onward, practically every collision of an F atom with RH at room temperature leads to reaction. The influence of the temperature on the reaction rate is therefore very small.

Investigations on the exchange reactions of F atoms with halogenated C_4 hydrocarbons show that the rate of the exchange reaction is practically independent of the position from which the Cl atom is eliminated, *i. e.* the rates of the reactions



(a) (b)

are roughly equal ($k_b/k_a=1.6$). The distribution of the internal energy must take place extremely rapidly[169].

Reactions of I atoms with hydrocarbons

$$I + RH \longrightarrow R^{\bullet} + HI$$

have recently been investigated in particular by *Benson et al.*[170]. The measurements are based on the following mechanism:

$$I_2 + M \rightleftharpoons 2I + M$$
$$RI + I \underset{b}{\overset{a}{\rightleftharpoons}} R^{\bullet} + I_2$$
$$R^{\bullet} + HI \underset{d}{\overset{c}{\rightleftharpoons}} RH + I$$

By making the plausible assumption that $E_b=0\pm1$ kcal/mole, it was possible to determine the enthalpies of formation of numerous hydrocarbon radicals from these investigations.

5.3. Excited Halogen Atoms

Halogen atoms have an important excited state ($^2P_{1/2}$), in which, in contrast with the excitation of atoms considered so far, there is no change in the spin state in relation to the ground state ($^2P_{3/2}$), but rather only a change in the total angular momentum. The energy difference between the two states increases with the atomic weight (see Table 9).

Table 9. Excitation energies for halogen atoms.

	$F(2^2P_{1/2})$	$Cl(3^2P_{1/2})$	$Br(4^2P_{1/2})$	$I(5^2P_{1/2})$
$E(^2P_{3/2} \rightarrow {}^2P_{1/2})$ ($kcal\ mole^{-1}$)	1.15	2.5	10.5	21.7

The greatest difference in reactivity is thus exhibited by $I(5^2P_{3/2})$ and $I(5^2P_{1/2})$ atoms. Thus the activation energy found for the reactions with C_2H_6 and C_3H_8[171]

$$I^*(5^2P_{1/2}) + C_3H_8 \longrightarrow C_3H_7^{\bullet} + HI \qquad (19)$$
$$k_{19} = 10^{10.3} \exp(-5.0/RT)\ cm^3\ mole^{-1}\ s^{-1}$$
$$I^*(5^2P_{1/2}) + C_2H_6 \longrightarrow C_2H_5^{\bullet} + HI \qquad (20)$$
$$k_{20} = 10^{10.4} \exp(-7.0/RT)\ cm^3\ mole^{-1}\ s^{-1}$$

are 19.4 kcal $mole^{-1}$ smaller than for the analogous reactions of iodine atoms in the ground state. However, the

greater reactivity of the excited states frequently is not evident, since deactivation is faster than the reaction.

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Systems of Monomolecular Layers—Assembling and Physico-Chemical Behavior

By Hans Kuhn and Dietmar Möbius[*]

Systems of monomolecular layers can form functional units having properties not exhibited by the individual layers. On UV irradiation, for example, an energy transfer takes place from a sensitizer (S) layer to an acceptor (A) layer and results in fluorescence of A. S and A may be cyanine dyes. Monomolecular layers can be manipulated in many ways and combined to construct novel systems; the energy transfer method can be used to establish whether the desired structure has in fact been produced. The monolayer assembling technique can also be used for the investigation of the deactivation of excited molecules; an interesting example is the spectral sensitization of the photographic process.

1. Construction of Organized Systems of Molecules with Monomolecular Layers as Structural Elements

It should be possible to construct functional units in molecular dimensions by fitting molecules together in a predetermined arrangement. Such systems, which have special properties that depend on the arrangement, are of interest as models for biological structures or as tools with structural elements having molecular dimensions. Their preparation requires the development of methods for linking intermolecular bonds similar to those available to the chemist for the planned formation of covalent bonds.

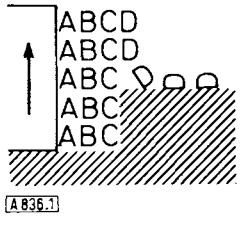


Fig. 1. Assembling monomolecular films of the molecules A, B, C, D.

There are several ways in which one could conceivably approach this ambitious goal. One possibility (Fig. 1) is to deposit a monomolecular layer of molecules A on a support, cover this layer with a monomolecular layer of molecules B, and cover this layer in turn with monomolecular layers of molecules C, D, *etc.* This would necessarily lead to a simple, organized system of molecules with a planned order on the molecular level in the direction perpendicular to the layer.

Monomolecular films of fatty acids on a water surface can be prepared by spreading[1]. A solution of the fatty acid is dropped on to the surface of the water. The solvent evaporates, and the fatty acid molecules left behind on the surface of the water are packed to a compact layer. The hydrophilic carboxyl group of each molecule is inserted in the water, while the zig-zag paraffin chains, which are extended perpendicular to the layer, are bound to one another by intermolecular forces. These layers can be transferred to a glass support[2].

Since functional units are made up from different components, molecular functional units in the sense of the objective outlined above cannot be produced with layers of fatty acids alone. By incorporating dye molecules into monomolecular layers[3], on the other hand, it is possible to build up complex systems according to a plan. The cyanine dye *(1)* has two long paraffin substituents and a hydrophilic chromophore. In a mixed layer with a long-chain fatty acid, *e.g.* arachidic acid ($C_{19}H_{39}COOH$), the paraffin substituents of the dye are firmly incorporated into the layer by interaction with the paraffin chains of the fatty

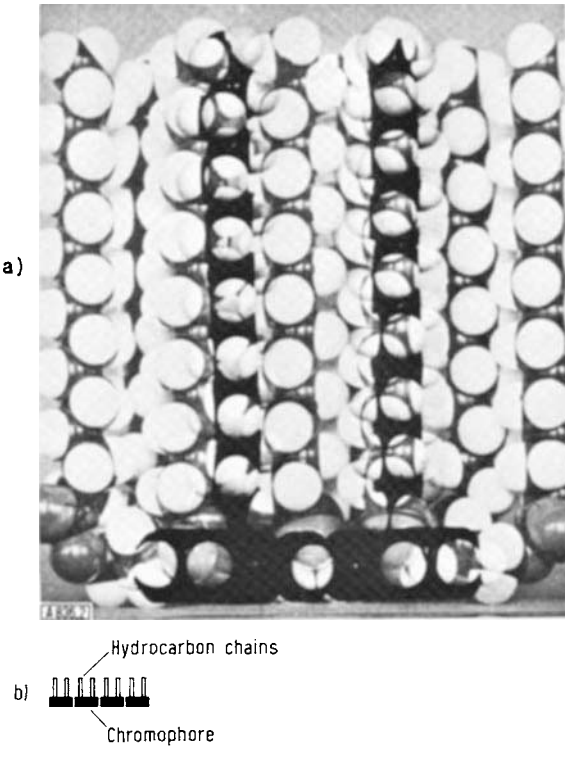
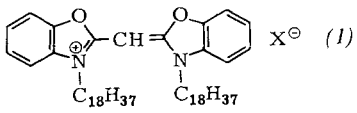


Fig. 2. (a) Model of a mixed layer of dye *(1)* and arachidate. The stearyl substituents of the dye molecule form a close-packed layer together with the arachidate molecules. (b) Symbol for such a layer (the arachidate molecules are not shown).

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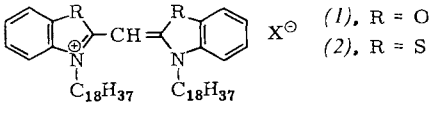
(1)

acid (Fig. 2). The hydrophilic chromophore is inserted in the water. This mixed layer is represented schematically as shown in Figure 2b, the fatty acid being omitted.

2. Energy Transfer in Layer Systems

2.1. System of a Sensitizer S and an Acceptor A as a Molecular Functional Unit

Layer systems can be built up by deposition of mixed layers containing dyes and fatty acid layers on suitable supports. The cross section through such a layer system is shown schematically in Figure 3. A few layers of arachidic acid were first deposited as a base on a glass plate (microscope slide). A layer of the dye *(1)* (S) was then applied over two thirds of the surface (zones 1 and 2), and a pure arachidic acid layer over the last third (zone 3). Zone 1 was now covered with a layer of arachidic acid, and zones 2 and 3 with five layers of arachidic acid. Finally, a mixed layer containing the paraffin-substituted cyanine dye *(2)* (A) was deposited on the entire surface.



(1), R = O
(2), R = S

To check that such a layer structure is not changed by rearrangement processes, it is necessary to find a method by which the distance between the layers of S and A can be determined in the range of 50 Å.

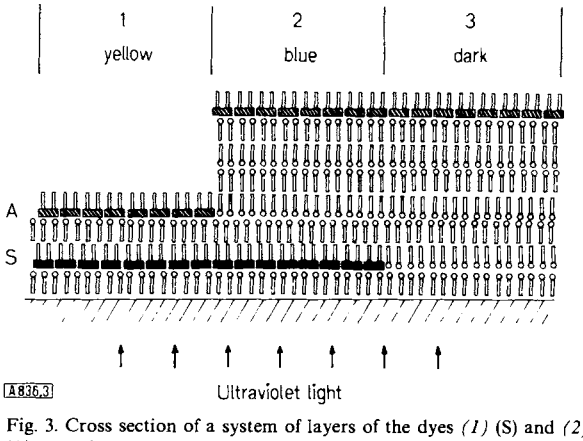


Fig. 3. Cross section of a system of layers of the dyes *(1)* (S) and *(2)* (A) on a glass support. The system is irradiated with ultraviolet radiation, which is absorbed only by S. Zone 1 (chromophores of S and A separated by 50 Å): energy transfer from S to A, yellow fluorescence of A. Zone 2 (S and A separated by 150 Å): blue fluorescence of S. Zone 3 (no S): no fluorescence. On irradiation with blue light, which is absorbed by A, all three zones exhibit the yellow fluorescence of A.

Such a method is provided by the Perrin-Förster energy transfer between dye molecules[4]. S is a dye that absorbs in the ultraviolet and fluoresces blue, while A absorbs blue and fluoresces yellow. If the system is irradiated with ultraviolet radiation, only S absorbs. In zone 2, where A and S are far apart, the blue fluorescence of S should appear. In zone 1, where the distance between A and S is 50 Å, energy transfer to A should take place, and the dye A should fluoresce instead of S. We therefore expect a yellow fluorescence. No fluorescence should occur in zone 3, since S is not present and A does not absorb ultraviolet radiation. This is experimentally confirmed[3, 5].

The system in zone 1 is an example of a simple molecular functional unit. The molecules S and A, which are fixed a short distance apart, have a property that is not exhibited by either of the individual molecules, *i.e.* they fluoresce yellow on excitation with ultraviolet light. The unit consisting of the molecules S and A acting together exercises a function that cannot be exercised by any of its parts alone, but only by the system consisting of both molecules as a whole.

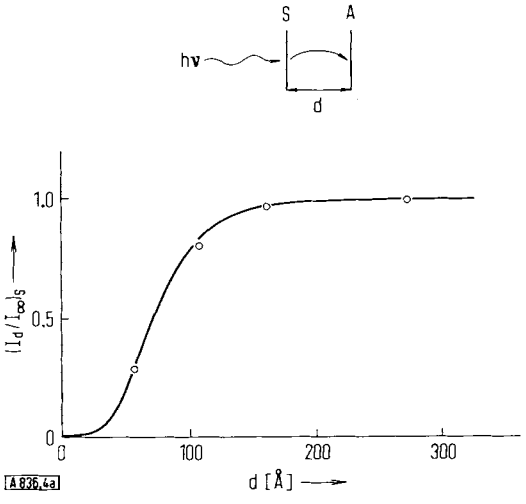


Fig. 4a. System of layers of the dyes S *(1)* and A *(2)* separated by a distance d. Intensity of the fluorescence of S plotted against d; the curve follows eq. *(1)* with $d_0 = 73$ Å.

The effect can be followed quantitatively and the Perrin-Förster theory verified[3]. Conversely, the good agreement between theory and experiment may be taken as indicating the presence of the planned order in the layer structure, and the diffusion of the dye molecules and the presence of holes in the layers can thus be ruled out. Figure 4a shows a plot of the fluorescence intensity of the sensitizer (I_d) against the distance d between the sensitizer and the acceptor layer[3]. The fluorescence intensity is zero, at short distances, and increases with increasing distance. The curve is given by the Förster theory. It follows the relation

$$(I_d/I_\infty)_s = [1 + (d_0/d)^4]^{-1} \quad (1)$$

where $d_0 = 73$ Å. The experimental points lie on the calculated curve. The parameter d_0 is given by:

$$d_0 = \alpha \frac{\lambda}{n} (q A_s)^{1/4} \quad (2)$$

In this equation, α is a steric factor, which depends on the orientation of the transition moments of the sensitizer and of the acceptor; in the present case, in which the transition

moments of S and A are randomly distributed in the plane of the layer, the value is found to be $\alpha = 0.0975$[6]. Also in eq. (2), λ is the wavelength of the fluorescence maximum of S, n is the refractive index of the medium (1.50 for cadmium arachidate layers), q is the quantum yield of the fluorescence of S, and A_s is the absorption of the acceptor layer (1-transmission) at the wavelength λ. In the case of a broad fluorescence band of S, the expression

$$A_s = \int_0^\infty f(\nu)\, A(\nu)\, (\nu_0/\nu)^4\, d\nu$$

has to be used for A_s. In this expression, $f(\nu)$ is the quantum spectrum of the fluorescence of S, normalized according to

$$\int_0^\infty f(\nu)\, d(\nu) = 1$$

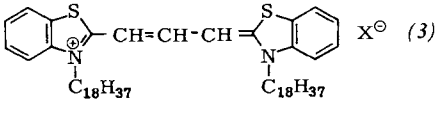
$A(\nu)$ is the absorption of the acceptor layer at frequency ν, and ν_0 is the frequency of the fluorescence maximum of S.

The parameter d_0 thus increases with increasing overlap of the fluorescence band of S with the absorption band of A and with increasing quantum yield q of the fluorescence of the sensitizer in the absence of the acceptor. From the experimental d_0 value, a value $q = 0.6$ is found for the case considered in Fig. 4a. This quantity q is the probability of the emission of a fluorescent light quantum by a molecule in the excited state from which the fluorescence can occur. q is relatively difficult to determine; it must lie between 1 and the value of the quantity q', where q' is the ratio of the number of quanta emitted by the dye layer per unit time as fluorescent light to the number of quanta absorbed by the dye layer per unit time.

In the earlier studies on energy transfer, q' and q were not distinguished, *i.e.*, q' was assumed to be equal to q. This agreement is not always found in layer systems. Cases are encountered in which q' and q differ considerably[7].

2.2. System of a Sensitizer S, a Primary Acceptor A, and a Secondary Acceptor A'

Figure 4b shows the results for a ternary system[8]. The same dyes *(1)* and *(2)* are used as the sensitizer S and the primary acceptor A as in the previous example; the secondary A' is the dye *(3)*, whose absorption band occurs in the position of the fluorescence band of A, and which therefore acts, according to the Perrin-Förster theory, as an acceptor for the excitation energy of A. The excitation energy transferred from S to A should thus pass on to the secondary acceptor A'.



(3)

The fluorescence intensity of the primary acceptor A is shown in Figure 4b as a function of the distance d' between the layers A and A'. For short distances d', the excitation energy is entirely transferred to the secondary acceptor A',

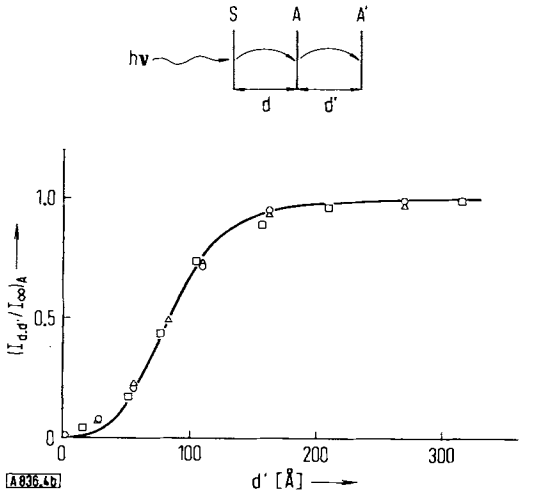


Fig. 4b. System of layers of the dyes S *(1)*, A *(2)*, and A' *(3)* separated by distances d and d', respectively. Intensity of the fluorescence of A plotted against the distance d' between the chromophores of A and A'. The distances d between S and A are 3 Å (squares), 27 Å (triangles), and 54 Å (circles). The curve follows eq. (1) with $d_0 = 83$ Å.

and the fluorescence of the primary acceptor A is quenched. For large distances d', the sensitized fluorescence of A is not quenched. The points lie on the calculated curve. This is found for various values of the distance d between the sensitizer S and the primary acceptor A.

3. Investigation of the Structure of Layer Systems by the Energy Transfer Method

3.1. Determination of the Thickness of a Cell Membrane

The thickness of the membrane of dried red blood cells, according to X-ray scattering measurements, is 80—85 Å[9]. The thickness can therefore be determined by the energy transfer method, which is particularly suitable for this range of distances[10]. A system with a fluorescent layer of the dye *(1)* at various distances over a thin vacuum-deposited layer of gold on a glass slide is first observed under the microscope. Figure 5 shows a photograph of the fluorescence of the cyanine dye *(1)*. The increase in the fluorescence with increasing distance from the gold layer (acceptor) is clearly seen.

Figure 6 shows the fluorescence of a layer system with a cell membrane incorporated. Such cell membranes are obtained by hemolysis of erythrocytes. The fluorescence

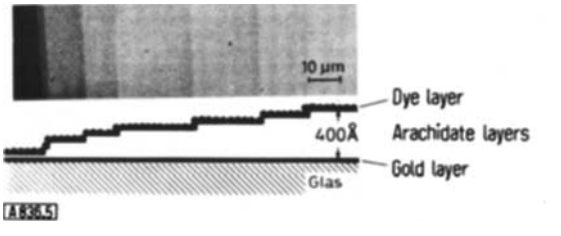


Fig. 5. Photomicrograph of the fluorescence of a layer of dye *(1)* situated at distances from a vacuum-deposited gold layer that increase from left to right; scheme of the layer system shown underneath. Strong quenching of the fluorescence at short distances as a result of energy transfer to the gold layer.

intensity of the dye layer is distinctly increased above the cell membrane because of the greater distance from the gold layer. Comparison with the fluorescence intensity of the dye layer at precisely defined distances from the gold

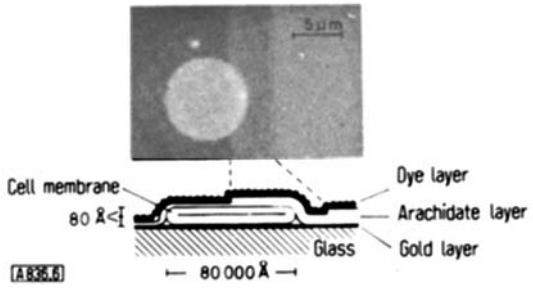
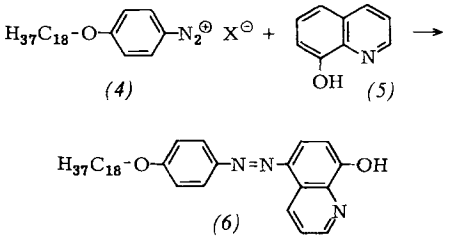


Fig. 6. Photomicrograph of the fluorescence of a layer of the dye *(1)* deposited on the system drawn underneath, which includes an erythrocyte membrane. The dye fluorescence is stronger over the erythrocyte membrane than in the adjacent zones because of the greater distance to the gold layer acting as the acceptor.

layer gave a value of 80 Å for the thickness of a membrane[10]. The feasibility of molecular contact between a monolayer assembly and a biological membrane allows new ways of interference of an organized system with the biological machinery.

3.2. Diffusion through Layer Systems

Small molecules can diffuse readily through a layer system. For example, a completely homogeneous layer of the azo dye *(6)* is formed from a layer of the diazonium salt *(4)* incorporated into a system when the coupling component *(5)* diffuses in and reacts with the salt *(4)*[11].



It is easy to establish by the energy transfer method whether a layer system built up over a diazonium salt is affected by such a process or remains unchanged.

To check this, the system shown on the left of Figure 7 is built up. The diazonium salt *(4)* is covered by only one layer of cadmium arachidate in zone 1, three layers in zone 2, and five layers in zone 3. The layer system is immersed in the solution of the coupling component *(5)*, and the azo dye *(6)* (A) is formed at the same rate in the three parts of the sample. A layer of the dye *(1)* (S) is then deposited over the system (Fig. 7, right-hand part).

The fluorescence of this dye layer is almost completely quenched in zone 1 because of energy transfer to the azo dye layer formed, strongly quenched in zone 2, and only weakly quenched in zone 3. It can therefore be concluded that the structure of the layer system is not changed by the diffusion of small molecules.

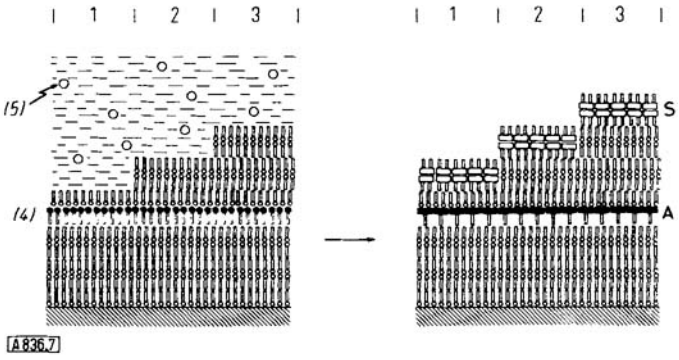


Fig. 7. Coupling reaction after diffusion of the coupling component *(5)* through the system of one (zone 1), three (zone 2), and five (zone 3) arachidate layers deposited on the diazonium salt *(4)*. After the reaction, the layer system is checked by deposition of a layer of dye *(1)* (S) and measurement of the fluorescence quenching of S. The test shows that the coupling component can diffuse in without damaging the layer system.

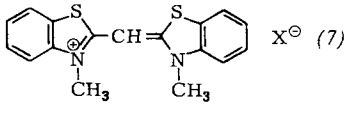
3.3. Adsorbed Monomolecular Dye Layers

In contrast with the fast diffusion of small molecules through layer systems, larger molecules, such as dyestuff ions, should not penetrate into a layer system, but should remain adhered to the surface of the system. In addition to the method we have already seen for producing organized systems by superposition of monomolecular films, this would now offer the possibility of obtaining such systems by adsorption of molecules on a monomolecular layer (Fig. 8).



Fig. 8. Formation of a system of layers of molecules A and B by adsorption of B from the substrate onto a spread monomolecular film of A.

To investigate the adsorption of dyestuff molecules, a layer of the dye *(1)* (S) is covered with a few layers of cadmium arachidate, and the system is immersed in a 10^{-5} M solution of the dye *(7)*. The layer of *(7)* adsorbed



on the surface of the system quenches the fluorescence of the incorporated dye layer.

Figure 9 shows a plot of the fluorescence intensity of the dye *(1)* against the distance d[12]. The experimental results agree well with the calculated values. Penetration of the adsorbed acceptor molecules would have caused stronger quenching of the fluorescence of the sensitizer, since the acceptor molecules *(7)* would have been closer to the sensitizer layer. This is found in systems with cadmium stearate layers instead of cadmium arachidate layers. The

fluorescence of the sensitizer is reduced to 50% at a distance four times as great as that expected. In systems with barium stearate instead of cadmium stearate, the dye molecules can penetrate even more readily into the layer system.

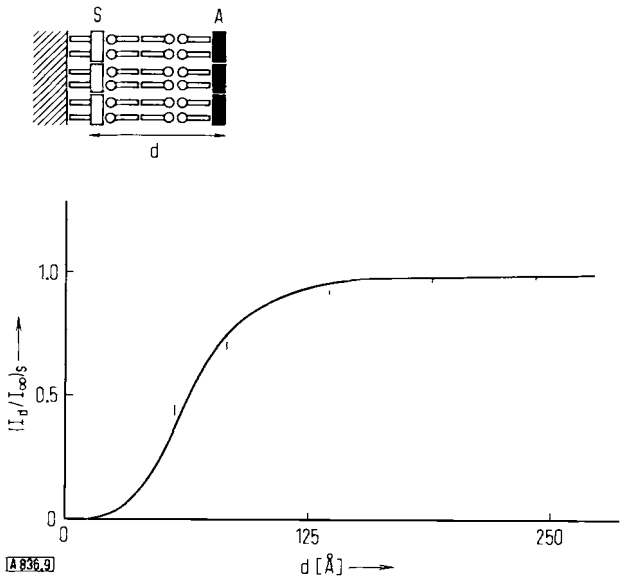


Fig. 9. Structure of a system consisting of a layer of the fluorescent dye S *(1)* and covering layers of arachidate after adsorption of the dye A *(7)* from aqueous solution. The fluorescence intensity $(I_d/I_\infty)_S$ of the layer of S is plotted against the distance d between the chromophores of S and of A. The curve follows the distance law for energy transfer [eq. (1)] with $d_0 = 64$ Å.

3.4. Lipid-Protein Layer Systems by Adsorption of Proteins

The possibility of obtaining organized systems by adsorption of molecules on a monomolecular layer is particularly interesting in the case of proteins that are to be incorporated into a layer system in the undenaturated form in connection with biological problems. The penetration of the protein into the monomolecular layer must be prevented, since this results in denaturation because hydrophobic groups of the protein are transferred from the interior of the molecule to the exterior. Penetration can be avoided by application of a sufficiently high surface pressure to the film on which the protein is being adsorbed. This is achieved by means of a device with which a monomolecular film can be held under any surface pressure and can be pushed to and fro on a water surface (Fig. 10)[13].

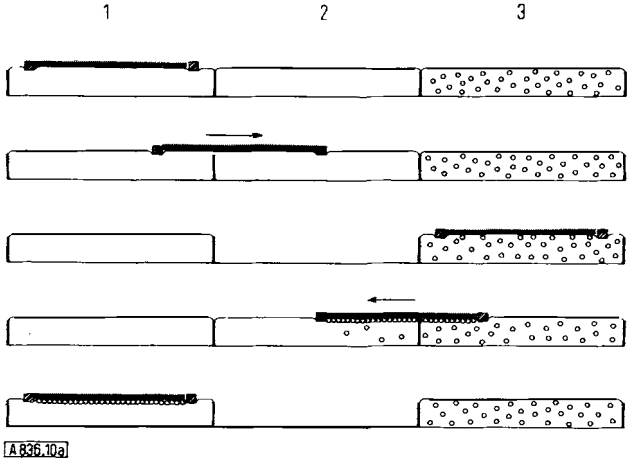




Fig. 10. Investigation of lipid-protein films. (a) Preparation of a lipid-protein film. The lipid film is spread on the water surface in compartment 1 and transferred to the surface of the protein solution in compartment 3. After adsorption of the protein film, the lipid-protein film is transferred back onto the protein-free substrate in compartment 1 for investigation. (b) Trough with six compartments for use in the operations described.

The monomolecular layer of fatty acid is produced in compartment 1. It is then pushed to compartment 2, which contains doubly distilled water as the subphase. The monomolecular layer is then moved to compartment 3, which contains a solution of the protein as the subphase. The film with the adsorbed protein is passed through compart-

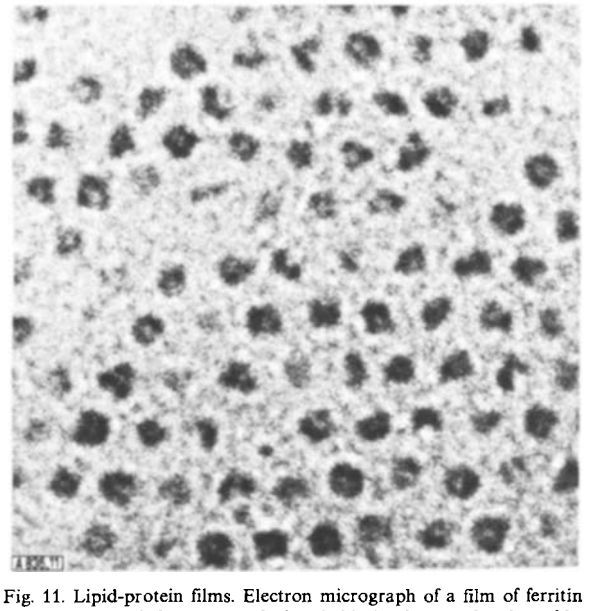


Fig. 11. Lipid-protein films. Electron micrograph of a film of ferritin adsorbed on methyl stearate and trimethyldodecylammonium bromide, molar mixing ratio 1:4. Spherical close packing of the protein molecules.

ment 2 to compartment 1 after a protein-free subphase has been introduced into both compartments. The surface pressure under which the film is held is measured by a Wilhelmy balance and kept to a preset value by a servo system that controls the slide.

The resulting layer of fatty acid with adsorbed protein can be transferred to a support, and its enzymatic activity can be measured[13]. In the case of the iron-rich protein ferritin, the adsorbed molecules can be seen directly under an electron microscope (Fig. 11)[14]. They are in a close packing arrangement.

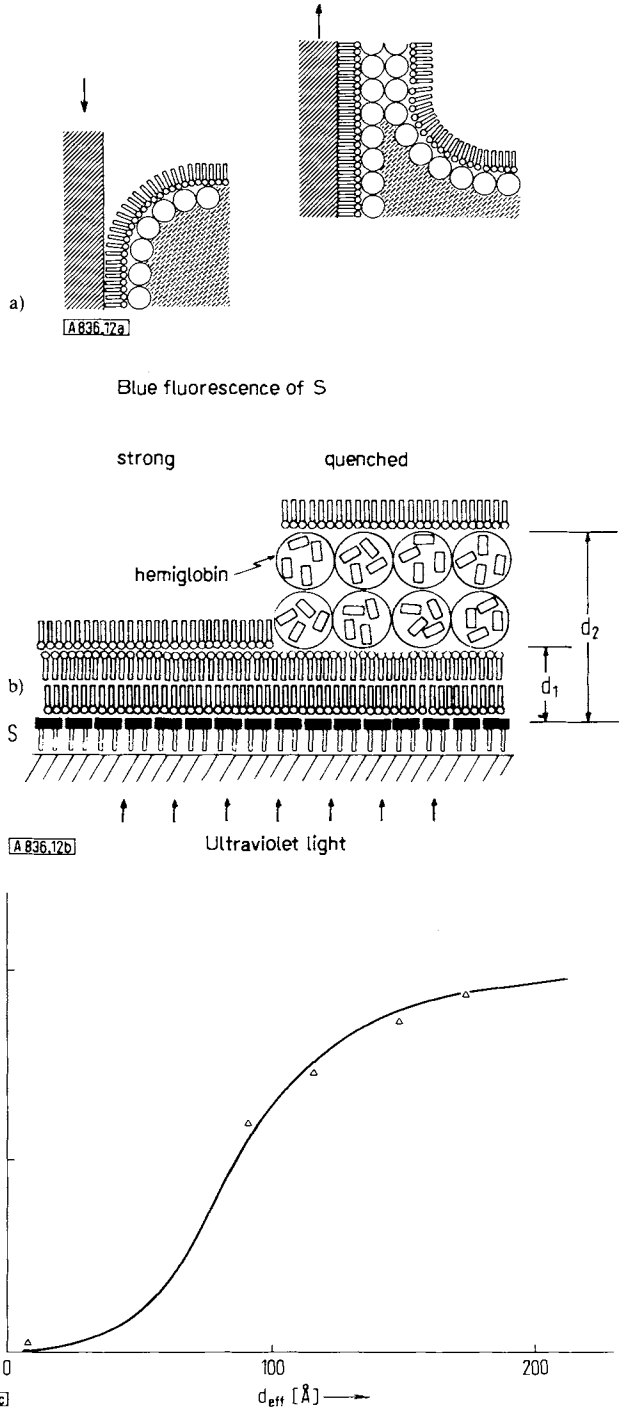


Fig. 12. Lipid-protein films in layer systems on glass. (a) Transfer of lipid-protein films to glass supports. (b) Layer system for the detection of the energy transfer from an excited layer of the dye S *(1)* to the heme groups of a hemiglobin double layer. (c) Intensity $(I_d/I_\infty)_S$ of the fluorescent dye layer as a function of the effective distance d_{eff} which is given by $1/d_{eff}^4 = (1/3)\,[(1/d_1^3) - (1/d_2^3)]\,[1/(d_2 - d_1)]$.

These monomolecular layers of lipid with adsorbed proteins can now be deposited on glass supports in the same way as the pure monomolecular lipid layers. For example, a layer structure may be produced as shown in Figures 12a and 12b[15]. The protein in this case is hemiglobin, which can be deposited as a double layer according to Figure 12a. In a layer system as shown in Figure 12b, the fluorescence in the right-hand section on excitation of the dye *(1)* with UV radiation should be considerably quenched by the energy transfer from the dye to the protein. This is in fact found.

Figure 12c shows the fluorescence intensity of the sensitizer S [dye *(1)*] as a function of the distance d_{eff} between the dye layer and a suitably defined center of gravity of the protein layer. Good agreement is found between the calculated curve and the experimental points. Another protein, *e.g.* plasma albumin, may also be deposited between the layers of the dye and the hemiglobin layer, and one can then check readily by the energy transfer whether the planned structure has been achieved[16]. It thus seems possible to build up functional units of several cooperating enzymes and to check the arrangement in this way.

3.5. Manipulation of Monomolecular Layers

Entirely new possibilities are opened up if a previously prepared layer system can be brought into molecular contact with a suitable surface in one step. To achieve this, one would have to be able to remove a monomolecular layer of the molecules B from the layer A, and to manipulate the layer B in such a way that it can be attached either from the underside or from above to a new monomolecular layer C (Fig. 13). The process can be readily checked at the various stages by the energy transfer method.

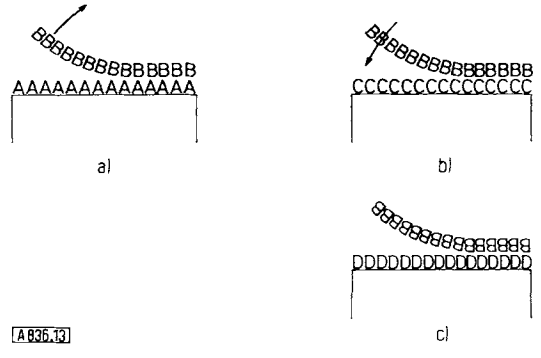
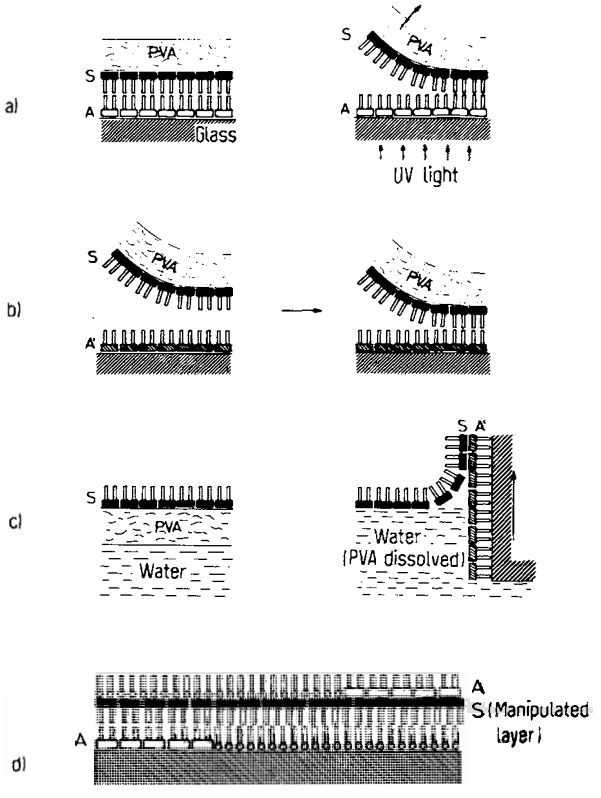


Fig. 13. Manipulation of monomolecular layers (schematic). (a) Complete separation of two monomolecular layers A and B. (b) Deposition of the separated layer B on another monomolecular layer C; molecular contact of B and C. (c) Deposition of the separated and inverted layer on another monomolecular layer D; molecular contact.

To achieve this aim, two monomolecular dye layers are superimposed on a glass support as described above; an aqueous solution of polyvinyl alcohol is then applied[17]. After drying, the polyvinyl alcohol foil can be removed from the glass support, and precise molecular separation of the layers occurs as shown in Figure 14a. To show this, the dyes are so chosen that one acts as the sensitizer [dye *(1)*], and the other as the acceptor [dye *(2)*]. As long as

the dye layers are in contact, energy is transferred to the acceptor on irradiation with light at the wavelength of the absorption band of the sensitizer, whereas energy transfer no longer occurs after separation of the layers. From the completely changed fluorescence observed after removal of the film, it can be concluded that the separation has taken place cleanly between the monomolecular layers of the sensitizer and of the acceptor (Fig. 14a).



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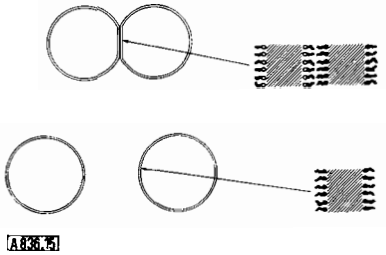
Fig. 14. Experimental procedure for the manipulation of monomolecular layers. (a) Complete separation of a monomolecular layer of S with a film of polyvinyl alcohol from a monomolecular layer of A on glass. (b) Molecular contact of the removed layer S with another layer A' after putting the polyvinyl alcohol film with the layer S on a plate with layer A'. (c) Removal of the polyvinyl alcohol film from the layer of S by application to a water surface and transfer of the inverted layer S to a support with a layer A'. (d) Checking the orientation of the transferred layer S and the molecular contact with adjacent layers A by investigation of the energy transfer from S to A.

If the polyvinyl alcohol film with one of the dyes is brought back to the support with the other dye or applied to a support carrying a monomolecular layer of another suitable dye, molecularly accurate contact is restored (Fig. 14b). This is shown by the fact that the fluorescence of the sensitizer is quenched at the contact area, while the sensitized fluorescence of the acceptor appears.

To bring the removed monomolecular layer of the sensitizer into molecularly accurate contact with another layer from the reverse side, as indicated in Fig. 13c, one proceeds as follows. The polyvinyl alcohol film is turned round, *i.e.* with the monomolecular layer of the sensitizer on top, and placed on a water surface. The polyvinyl alcohol layer dissolves (Fig. 14c). To show that the process proceeds as planned, the layer of S can be built into a layer system (Fig. 14d, see also Section 2.1). The manipulated layer with sensitizer dye S is brought into contact on its hydrocarbon side with an acceptor dye A in zone 1 of the plate, and on its chromophore side in zone 3. On UV-irradiation, stronger quenching of the fluorescence of the sensitizer S and stronger sensitized fluorescence of the acceptor A are to be expected in zone 3 than in zone 1, since the chromophores of S and A are in direct contact in zone 3, whereas they are separated by paraffin chains in zone 1. The unquenched fluorescence of S should appear in zone 2. This behavior is in fact observed.

This technique can also be used in the case of layer systems with complicated structures. It is possible to divide a system of suitable architecture between precisely determined layers.

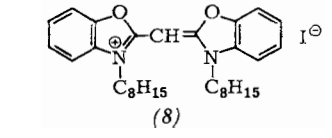
Another method of bringing layers into molecular contact and separating them again is by contact and subsequent separation of two soap bubbles. It has been an open question in this case whether such a process takes place in accordance with Figure 15, *i.e.* without diffusion of the molecules from one of the monomolecular layers into the other, or whether rearrangement of the layers occurs. To check this, different fluorescent surface active dyes, *e.g. (8)* and *(9)*, are incorporated into the two soap lamellae. The energy transfer can be investigated with such dyes just as in the layer system described above[18]. It is found that no rearrangement of the layers and no diffusion of dye molecules from one lamella into the other take place during short contact



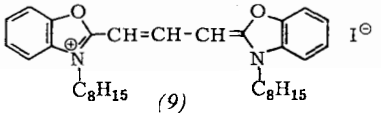
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Fig. 15. Double sandwich structure at the contact surface between two soap bubbles. No diffusion of molecules of one soap bubble into the other occurs on separation of the soap bubbles, as is shown by the investigation of the energy transfer between the dyes incorporated into the soap bubbles.

times. The soap lamellae in contact with each other have the double-lamella structure shown in Figure 15. They thus form a bimolecular lipid membrane in the contact zone between two aqueous phases[18].



(8)



(9)

Bimolecular lipid membranes play an important role in biological systems. The experiments described offer a new possibility of producing models of such membranes. Since molecularly accurate separation can be achieved between

the two layers, it must be possible to study permeation processes with radioactive indicators. Unsymmetrical membranes, which were unobtainable by earlier methods[19], and which are of interest as models of biological membranes, can be prepared by this method.

4. Investigation of the Deactivation of Excited Molecules by the Monolayer Assembling Technique

4.1. Deactivation Pathway in Singlet-Triplet Transitions

An excited dye molecule may be deactivated in such a way that it passes through the lowest vibronic level of the first excited singlet state, or that it avoids this state. The transition to the triplet system can take place from this state (Fig. 16a) or from a higher vibronic level of the excited

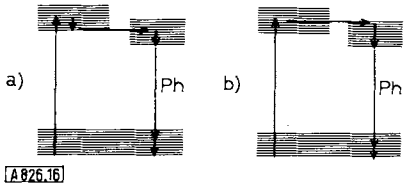
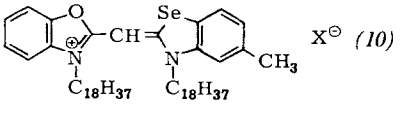
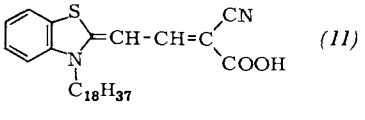


Fig. 16. Deactivation of an excited molecule by emission of phosphorescence. Transition from the singlet to the triplet system (a) from the lowest vibronic term of the first excited singlet state, (b) avoiding this term.

singlet state (Fig. 16b). In the case of deactivation according to Figure 16a, the fluorescence emission occurs in competition with the transition to the triplet system. A specific fluorescence acceptor reduces the population of the state from which the fluorescence takes place, and hence also the population of the triplet state. The phosphorescence that takes place from the triplet state to the ground state is thus quenched by the fluorescence acceptor. In the case illustrated in Figure 16b, on the other hand, the probability of the transition to the triplet system is independent of the population of the state from which the fluorescence takes place. A specific fluorescence acceptor thus does not affect the phosphorescence intensity.



(10)



(11)

In the case of the dye *(10)*, the fluorescence is practically completely quenched by application of a layer of the specific fluorescence acceptor *(11)* at a distance of *e.g.* 80 Å, while the intensity of the phosphorescence is reduced only to about half. It may be concluded from the dependence of this effect on distance that the pathways in accordance with Figures 16a and 16b are involved in a ratio of 6:4 in the deactivation of S [dye *(10)*][20]. In contrast with the general view, therefore, the pathway according to Figure 16b cannot be disregarded in comparison with that according to Figure 16a.

4.2. Deactivation of an Excited, Nonfluorescent Dye

An optically excited molecule can be deactivated by emission of fluorescence or by radiationless processes. In the case of a dye that emits no detectable fluorescence, radiationless deactivation processes predominate. In the presence of an acceptor, energy transfer competes with these processes. The emission of a sensitized fluorescence is therefore to be expected in the case of a fluorescent acceptor.

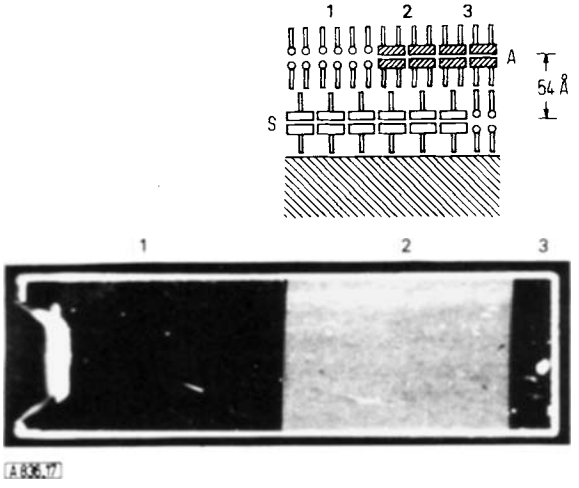
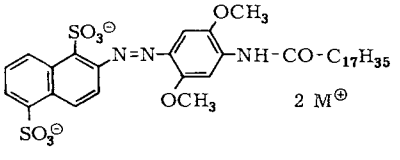
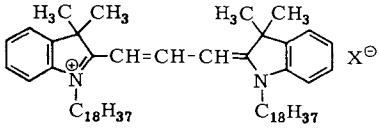


Fig. 17. Sensitized fluorescence of an acceptor layer A after energy transfer from a nonfluorescent sensitizer layer S at a distance of 54 Å. Structure of the sample (top, schematic), photograph of the fluorescence on excitation with violet light ($\lambda = 405$ nm, bottom). Zone 1: S only, no fluorescence; zone 2: sensitized fluorescence of A (red), zone 3: S missing, no fluorescence.

Figure 17 shows a photograph of the fluorescence of a system containing a layer of the azo dye *(12)* (S) and a layer of the fluorescent cyanine dye *(13)* (A) separated by a distance of 54 Å on excitation with blue light. Zone 3 of



(12)



(13)

the sample has no azo dye layer; no fluorescence is observed in this region, whereas the sensitized fluorescence of A is distinctly visible in zone 2. Zone 1 has no A, and exhibits no fluorescence[21].

The distance law, and hence the important parameter d_0, can be determined by measurement of the relative intensities of the sensitized fluorescence. The intensity I_d of the

sensitized fluorescence of A for a distance d between the layers of S and A should then theoretically be given by the relation[22]:

$$(I_d/I_0)_A = [1 + (d/d_0)^4]^{-1} \quad (3)$$

where d_0 is related to q by eq. 2 in Section 2.1.

The energy transfer method thus allows the determination of the quantity q, even in cases of sensitizers that do not emit detectable fluorescence. For the azo dye considered here, it was found that $q = 0.003$[21].

The lowest vibronic level of the singlet excited state of the azo dye can be depopulated by the acceptor, and one can therefore deduce from the intensity of the sensitized fluorescence how many molecules of the nonfluorescent dye have reached this state. By comparison with the number of primarily excited molecules, it is possible to calculate the probability p with which an excited molecule reaches the lowest vibronic level of the excited singlet state. It was found that $p = 0.2$. The quantum yield q' of the azo dye that does not exhibit detectable fluorescence is therefore[21]

$$q' = p \times q = 0.2 \times 0.003 = 6 \times 10^{-4} \quad (4)$$

4.3. Determination of the Multipole Nature of the Emitter by the Energy Transfer Method

For the description of the luminescence and of the energy transfer, it is useful to describe the radiating molecule as an antenna, which gradually dissipates its energy *via* the electromagnetic field or transfers it to the acceptor. Though the emission of light is in reality a discrete process, the classic approach is useful, since it is particularly simple, and the results can be readily translated into the language of the quantum theory. The radiation power L_e given by the classical model can be used to find the probability dW with which the excited molecule emits the light quantum (energy $h\nu$) in the time dt:

$$dW/dt = L_e/h\nu \quad (5)$$

The probability that light is manifested to the usual detectors as a light quantum in a given space and time interval is given by the electric field strength in the electromagnetic field.

A fluorescent molecule can always be described as an oscillating electric dipole, since the fluorescence corresponds to an allowed transition. In phosphorescence (a forbidden transition from the triplet excited state to the ground state of the dye), practically nothing is known about the multipole nature[23]. It is conceivable that the molecule behaves as an electric dipole emitter, but also as a magnetic dipole emitter or an electric quadrupole emitter. In addition to L_e, it is necessary to consider the power L_t that the molecule dissipates radiationlessly to its environment. The quantum yield q defined in Section 2.1 is then determined by the two quantities:

$$q = L_e/(L_e + L_t) \quad (6)$$

An acceptor molecule is now brought to a point at which the electric field strength in the electromagnetic field of the oscillating emitter has the amplitude F_0. The power L_a absorbed by the acceptor is[6]

$$L_a = aF_0^2 \quad (7)$$

where a is a constant.

If the distance r between the emitter and the acceptor is small compared with the wavelength of the luminescence, F_0 is given directly by Coulomb's law or the induction law (Fig. 18). F_0 is proportional to $1/r^2$ for magnetic dipoles, proportional to $1/r^3$ for electric dipoles, and proportional to $1/r^4$ for electric quadrupoles. The power L_a absorbed by a planar layer of acceptors is found by summation over the contributions of all the molecules in the layer. The parameter a introduced above is a measure of the power absorbed by an acceptor molecule in a field alternating with frequency ν. Its value is related to the extinction coefficient of the molecule for light of frequency ν.

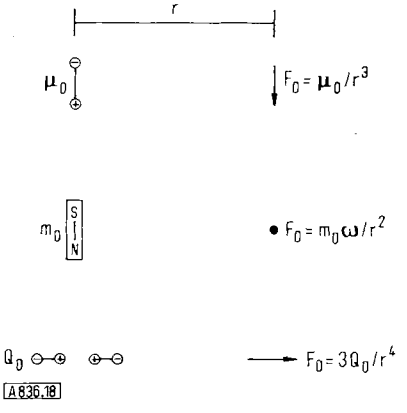


Fig. 18. Oscillating emitters [electric dipole (amplitude μ_0), magnetic dipole (amplitude m_0), circular frequency $\omega = 2\pi\nu$), and electric linear quadrupole (amplitude Q_0)] and amplitude F_0 of the electric field strength at a distance r from the emitters (r small in relation to the wavelength of the luminescence).

The fraction of the energy of the excited molecules that is emitted in the presence of the acceptor is given by the ratio $L_e/(L_e + L_t + L_a)$. Since the energy transfer to the acceptor competes with the emission of radiation and with the radiationless deactivation in the molecule, the average lifetime of the excited state (τ_d), and hence the decay time of the luminescence, is inversely proportional to this ratio. For an acceptor layer having absorption A, we obtain the relation[6, 24]

$$(\tau_d/\tau_\infty)_S = [1 + (d_0/d)^p]^{-1} \quad (8)$$

with

$$d_0 = \alpha \frac{\lambda}{n} (qA)^{1/p}$$

where $p = 2$ for a magnetic dipole, $p = 4$ for an electric dipole, and $p = 6$ for an electric quadrupole. α is a steric factor, which can assume values between 0.069 and 0.21[24], λ is the wavelength of the luminescence, and the quantum yield q may lie between the value 1 and the value of q' (Section 2.1).

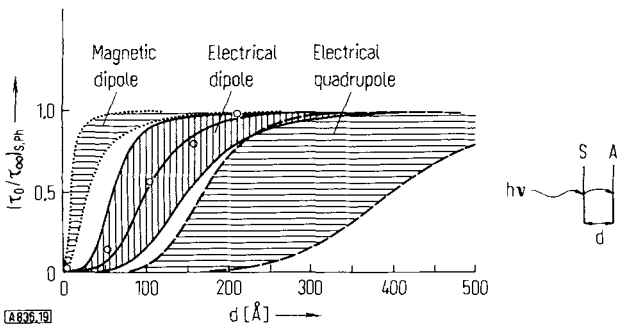
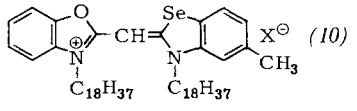
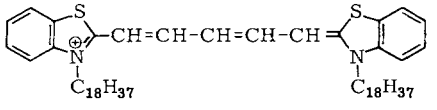


Fig. 19. Decay time $(\tau_d/\tau_\infty)_S$ of the phosphorescence of a layer of S [dye *(10)*] plotted against the distance d from the layer A [dye *(14)*]. Circles: experimental values. The experimental values must lie within the shaded areas for the given emitter types for this system of S and A: the emission of phosphorescence by S is therefore attributable to an electric dipole transition.

Insertion of the experimental values for the example investigated, with the largest and smallest possible values for α and for q, gives the curves in Figure 19 when τ_d is plotted against d. As can be seen from the figure, the quantity d_0 is at most 30 Å for a magnetic dipole, at least 170 Å for an electric quadrupole, and between 60 and 150 Å for an electric dipole. A decrease in the decay time of the phosphorescence can in fact be detected at greater distances[24].



(10)



(14)

The experimental points (Fig. 19) lie on the curve expected for the electric dipole, and a value of $d_0 = 100$ Å is found. This experimental value shows that an electric dipole transition predominates in the case considered here.

The result was confirmed by a second method based on the monolayer assembling technique[24,25]: By measurement of the angular dependence of the phosphorescence emitted by a monomolecular dye layer at an accurately fixed distance in front of a reflecting metal surface.

It would be interesting to realize the other cases experimentally, particularly that of the electric quadrupole emitter, in which the energy transfer should be possible over considerably greater distances than in the case of the electric dipole emitter.

4.4. Luminescence Lifetime of a Molecule in the Vicinity of the Interface between Dielectrics with Different Polarizabilities

The lifetime of the excited state of a molecule is shortened by transfer of part of the excitation energy to the acceptor, with the result that the quantum yield of the luminescence is decreased. Using the monolayer assembling technique it is possible to demonstrate the surprising effect that the lifetime can also be changed without variation of the luminescence quantum yield. The lifetime depends on the distance of the emitter from the interface between dielectrics with different polarizabilities[26-28].

To understand this effect, we again use the classical model for the sake of simplicity, and we again consider first the energy transfer from an excited molecule S, which may be described as a dipole oscillator, to an acceptor molecule A, which is situated in the alternating electric field of this oscillator (Fig. 20). In the classical approach, the oscillator

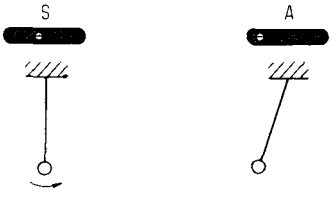


Fig. 20. Classical model of energy transfer. The acceptor molecule A is situated in the electric field of the oscillating dipole S. A oscillates under the influence of S with a phase shift relative to S, and dampens S: energy is transferred from S to A.

A may be described as a damped pendulum, which co-oscillates under the influence of the oscillator S, but with a phase difference with respect to the latter. The field of A in turn acts on the oscillator S and dampens it, so shortening its decay time. In the classical approach, energy is transferred from S to A.

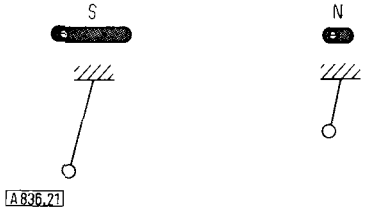


Fig. 21. Classical model of energy transfer. The nonabsorbing molecule N oscillates in phase with S, and does not dampen S: no energy is transferred from S to N.

If A is replaced by a nonabsorbing molecule, the corresponding oscillator is in phase with S, and it then has neither a dampening nor an accelerating effect (Fig. 21). But, this is not quite true, since the field of S takes a certain time to reach the nonabsorbing molecule, and a certain time is also required for the field from the oscillating nonabsorbing molecule to reach the position of S[6]. A certain phase shift thus results between the movement of the oscillator and the field from the induced oscillator. This echo reaches S only after a delay due to the finite propagation velocity of the electromagnetic field, and has an accelerating or retarding effect on the oscillator S, depending on the phase relation between the elongation of S and the echo field. Though the induced oscillator in this case absorbs no energy once it has been induced, the decay time of S is shortened or increased according to the phase relation. The initial excitation energy of the oscillator S is completely emitted as radiation; however, this process takes a shorter or longer time, according to the phase relation.

In the case of Figure 20, the power L_a is the decisive factor, and the effect of the co-oscillating charge of A on L_e is

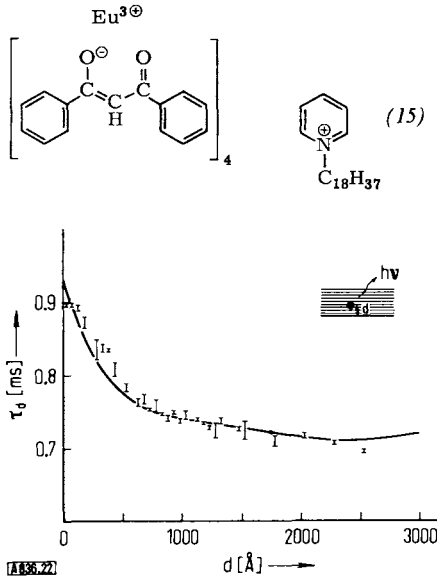


Fig. 22. Lifetime τ_d of the excited state of the luminescent europium complex *(15)* in a layer system as a function of the distance d between the layer of the complex and the interface between the layer system and air. The curve is found on assumption of an isotropic oscillator.

negligible. In the case of Figure 21, $L_a = 0$, and the power L_e emitted by the system as a whole depends on the distance between the oscillator S and the induced oscillator.

Instead of one nonabsorbing molecule, let us now consider many such molecules, *i.e.* a dielectric that is assumed to extend over the shaded area in Figure 22. The induced fields of each molecule add together, and the average lifetime of the sensitizer S is therefore a function of the distance d of the molecule from the interface. A simple relation[28], which is plotted in Fig. 22 for the case $q = 1$, is found for the lifetime τ_d of the luminescence of an isotropic oscillator.

Such an arrangement can be produced by incorporating the luminescent molecules into a layer system. The system is then excited by a light pulse, and the decay time of the luminescence is measured for different values of the distance d between the luminescent molecules and the interface between the layer system and air. The lifetime of the excited state as a function of the distance d is shown in Figure 22 for the europium complex *(15)*. The quantum yield has a very strong effect, and the agreement between the experimental and calculated values confirms the above value $q = 1$. The method should be of interest for the determination of the quantum yield q of the luminescence of the molecule in the luminescent state. Another method for the determination of q, which was described in Section 2.1, also gives the value $q = 1$ in the present case[3].

The emission of a light quantum by a molecule excited at time 0 is a stochastic process. It occurs earlier in one case and later in another, but one can speak of an average lifetime of the excited state. The fact that this average is not a constant of the molecule, but depends on the distance of the molecule from the interface (*i.e.* on the broad environment of the molecule), seems very surprising at first sight, but is immediately obvious in the above classical picture. The wave/particle duality of light is very clearly demonstrated by this result[29].

4.5. Primary Processes in Spectral Sensitization of Photographic Material

Silver bromide is practically insensitive to yellow or red light; a dye must be adsorbed on its surface to sensitize it (Fig. 23a). The dye molecule absorbs a quantum of light, and the electron that then passes into the conduction band of the silver bromide diffuses to an imperfection, where the nucleus of the latent image is formed. The reduction to metallic silver begins at this nucleus during the development process.

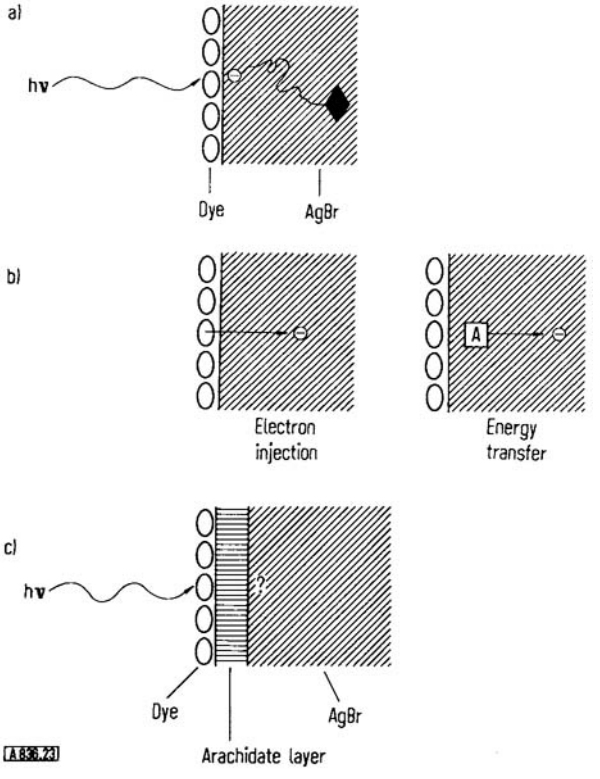


Fig. 23. Spectral sensitization of AgBr by a dye layer. (a) After absorption of light by the dye layer, a nucleus of the latent image is formed in the AgBr crystal. (b) Proposed mechanisms of spectral sensitization by excited dye molecules: electron injection into the conduction band of AgBr; energy transfer to acceptors in the boundary zone of the AgBr crystal, which then deliver an electron into the conduction band. (c) Method of differentiating between these mechanisms: suppression of electron injection by an arachidate layer between the dye and the AgBr.

Two hypotheses have been proposed[30] regarding the formation of this conduction electron (Fig. 23b). According to the electron injection hypothesis, this electron originates in the dye. The electron that was promoted into a higher orbital of the dye molecule on absorption can tunnel into the AgBr. According to the energy transfer hypothesis, energy acceptors are situated in the vicinity of the surface of AgBr. After the absorption of the light quantum by the dye molecule, the excitation energy is transferred to such an acceptor. The excited acceptor can deliver an electron to the conduction band of the silver bromide.

The two possibilities are easily distinguished by fixing the dye molecule at a given distance, *e.g.* 30 Å, from the surface of the silver bromide (Fig. 23c). From the foregoing discussion, the energy transfer can take place readily over such a distance, whereas the tunneling of the electron becomes extremely improbable[31]. The dye molecule can be fixed at accurately defined distances from the AgBr surface by

the monolayer assembling technique with interposition of one or more layers of fatty acid. The system is exposed and developed, and one then observes whether a photographic image is produced. The image density is a measure of the sensitization s by the dye.

In Figure 24a, the distance b between the dye layer and the surface of the silver bromide is plotted on the abscissa,

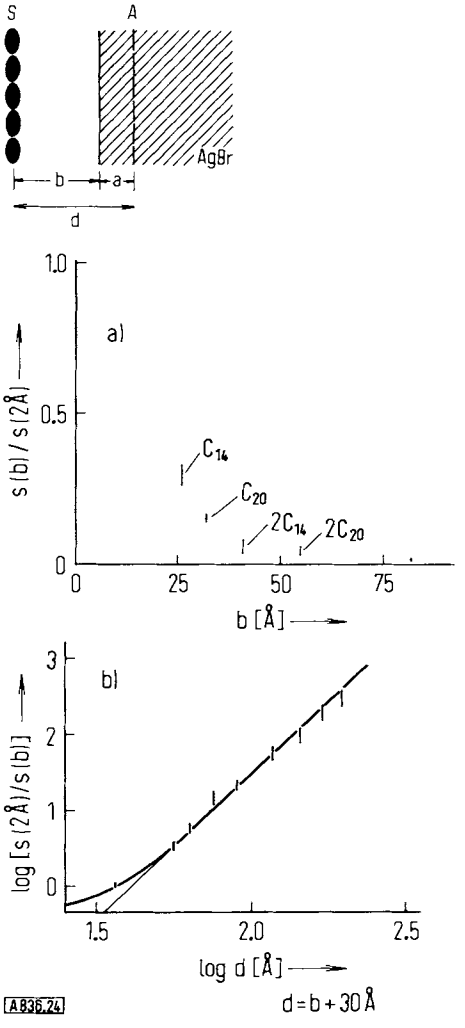
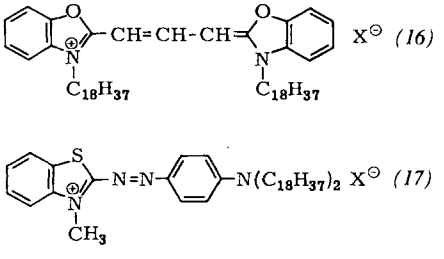


Fig. 24. Spectral sensitization of vacuum-deposited AgBr layers by a monomolecular layer of the dye *(16)* (S). (a) Sensitization $s(b)/s(2\text{ Å})$ as a function of the distance b from the dye chromophore to the AgBr surface (C_{14} = myristic acid, C_{20} = arachidic acid). (b) log $[s(2\text{ Å})/s(b)]$ as a function of the distance $d = b + 30$ Å between an assumed model acceptor layer and the dye chromophores. The curve shows the dependence expected from the energy transfer model. The slope of the straight line, corresponding to this model, is $p = 4$.

while the ratio of the sensitization $s(b)$ at distance b to the sensitization $s(2\text{ Å})$ with direct contact is plotted on the ordinate[32]. The desired distances are obtained by means of one or several monomolecular layers of C_{14} or C_{20} fatty acids. The figure shows that a distinct sensitization occurs at these distances, and decreases with increasing distance b.

The spectral sensitization of the photographic process can be investigated quantitatively at distances up to 300 Å. It is then weaker by a factor of about 1000 than with direct contact, but still large in comparison with the intrinsic sensitivity of silver bromide to the irradiated light of wavelength 500 nm. A photographic image that can be quantitatively evaluated can therefore be obtained by simply exposing for a sufficiently long time at a sufficiently high intensity.

The reciprocal of the sensitization is plotted in Figure 24b in a double-logarithmic graph against the distance d between the dye layer and the hypothetical layer of acceptors in the silver bromide. It is assumed here that these acceptors are situated at an average distance a of about 30 Å below the surface of the silver bromide. The curve agrees with expectations based on the Perrin-Förster theory of energy transfer, according to which s is proportional to $[1+(d/d_0)^4]^{-1}$. d_0 is the distance between the sensitizer and acceptor layers at which every second excited sensitizer molecule just loses its excitation energy by energy transfer to the acceptor. The figure shows the good agreement between theory and experiment over this wide measurement range. The slope of the tangent to the curve gives the exponent in the distance law, and the expected value of 4 is obtained. The intercept of the tangent with the abscissa gives a value of 54 Å for the quantity d_0. The absorption A_s (1-transmission) of the hypothetical acceptor layer at the wavelength of the emission of S can be calculated from the value of the quantity d_0 [cf. eq. (2), Section 2.1]. d_0 is proportional to $A_s^{1/4}$, and one obtains the value $A_s = 10^{-4}$. Since this value is so small, direct spectroscopic identification of these hypothetical acceptors in silver bromide has not yet been accomplished.



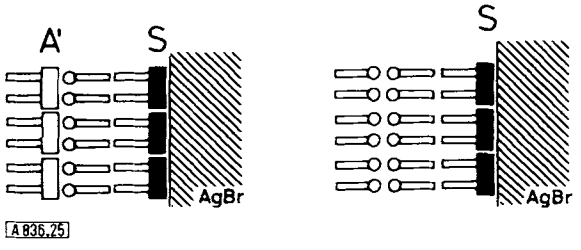


Fig. 25. Effect of a competitor A' [dye *(17)*] for the acceptors in AgBr. A' reduces the sensitization of the photographic process by S [dye *(16)*]. The agreement of the experimental reduction with that calculated on the basis of the energy transfer model shows that there is no electron injection from the excited sensitizer into the AgBr in this case.

As a further check of these results, let us consider a system in which the sensitizer [dye *(16)*] adheres to the surface of the silver bromide, and in which a monomolecular layer of the dye *(17)* (A') is situated at a distance of about 50 Å from the sensitizer layer[32] (Fig. 25). A' is so chosen that it acts as an acceptor for the excitation energy of S, *i.e.* its absorption band overlaps with the fluorescence band of S. A' should therefore compete with the energy acceptors in the silver bromide, and so reduce the sensitizing action of S. It is possible to calculate the amount by which the sensitization should be reduced at the given distance; the reduction is in fact found to be as expected.

If electron injection also played an important part in the case of direct contact, the energy acceptors A′ would be less effective as competitors.

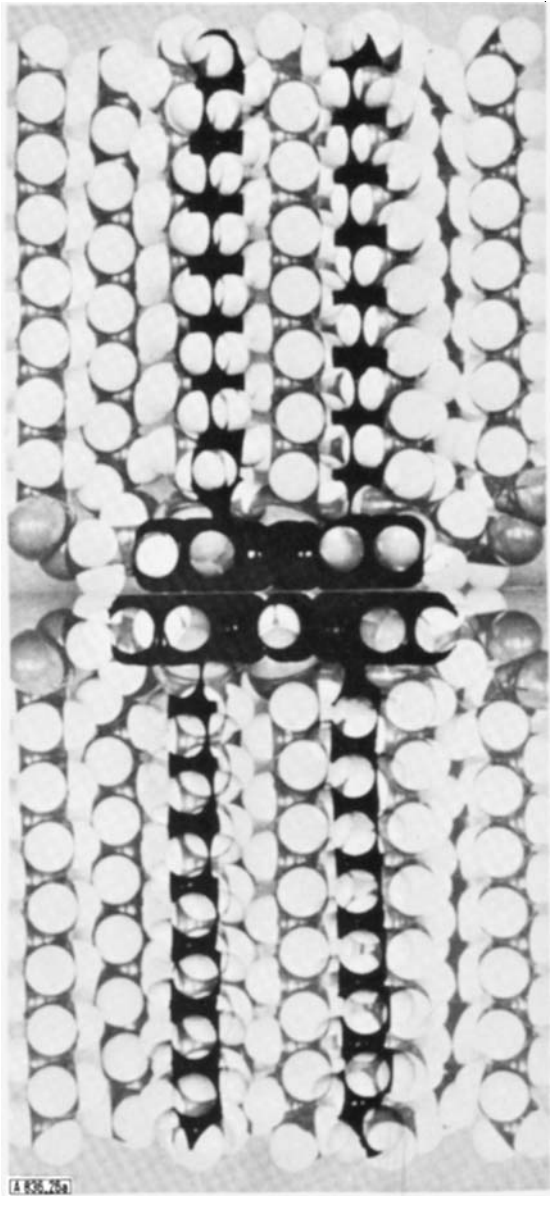
$s_{\text{without A'}}/s_{\text{with A'}} = 1.4 \pm 0.2$ (calc. 1.4)

The results obtained can thus only be explained by the energy transfer hypothesis. It is not yet known how far generalization of the results to other cases of photographic sensitization is possible.

5. Light Absorption by Dye Aggregates in Monomolecular Layer Systems

5.1. Absorption by Sandwich Aggregates

The weak interaction between relatively distant molecules has been discussed above. We shall now examine the interaction between adjacent dye chromophores. The monolayer assembling technique offers a possibility of positioning chromophores sandwich-like one over another[29]. It is possible in this way to produce systems in which the chromophores of the same dye or of different dyes are in direct contact, while the paraffin substituents are anchored in the layers (Fig. 26a). These systems give absorption spectra in which the interaction between the chromophores is reflected.



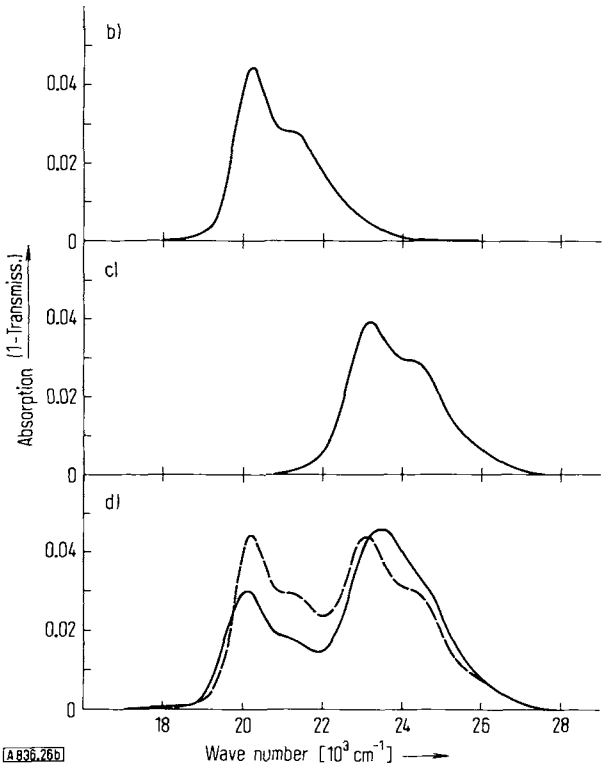


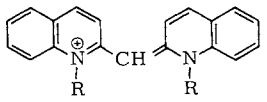
Fig. 26. Formation of mixed dimers of cyanine dyes in sandwich systems of monomolecular layers. (a) Model of a pair of molecules in mixed layers. Absorption as a function of the wave number (b) and (c) in the case of isolated chromophores of the dyes *(16)* and *(2)*, respectively, (d) in the case of molecule pair formation (full curve). The broken curve is the sum of the spectra of (b) and (c).

The absorption spectrum given by the pair of dyes *(16)* and *(2)* is shown by the continuous curve in Figure 26d, while the broken curve is the result of superposition of the absorption spectra (Fig. 26b and 26c) of the individual dye layers[33]. In the case of the pair, the long-wave band is weakened and displaced to longer wavelengths, while the short-wave band is intensified and displaced to shorter wavelengths. This effect can be understood from the coupled oscillator model. This model represents the result of the quantum mechanical calculation, by which the coupling coefficients of these oscillators are evaluated. With the electron gas model the band shifts and intensity changes due to aggregation have been calculated in a number of cases and the differences between experimental and theoretical values were less than 30%[33].

5.2. Absorption of Scheibe Aggregates

This model is applied below to Scheibe dye aggregates[34], *i. e.* to aggregates of dye molecules that have a very narrow, intense absorption band and a narrow fluorescence band that practically coincides with the absorption band[35].

According to *Förster*[36], this band may be assigned to an in-phase oscillation of the equivalent oscillators of all the dye molecules of the aggregate. In the case of the Scheibe pseudoisocyanine [dye *(18)*], the narrow band of the



(18), R = C_2H_5
(19), R = $C_{18}H_{37}$

associate is displaced by 53 nm to longer wavelengths as compared with the monomer band in aqueous solution. The calculation gives the opposite sign for the structures proposed so far[37], *i.e.* the "staircase" or the "ladder" arrangement (Fig. 27), and the same sign but a much smaller value for a structure proposed by *Bird et al.*[38].

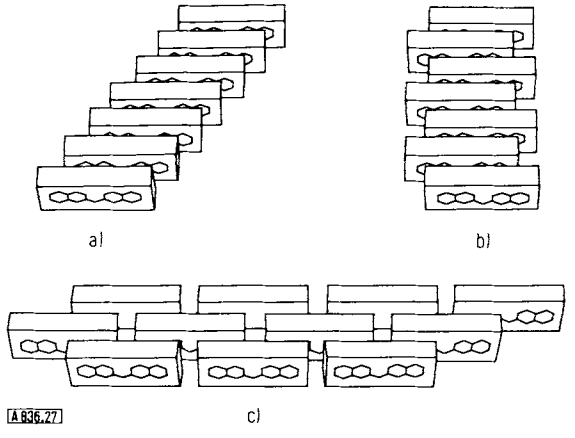


Fig. 27. Structural model for Scheibe aggregates of the cyanine dye *(18)*. (a) Staircase model (−40), (b) ladder model (−52), (c) brickwork arrangement (+44). The figures are the theoretically expected shifts ($\lambda_A - \lambda_M$) of the aggregate band in relation to the monomer band in the absorption spectrum given in nm.

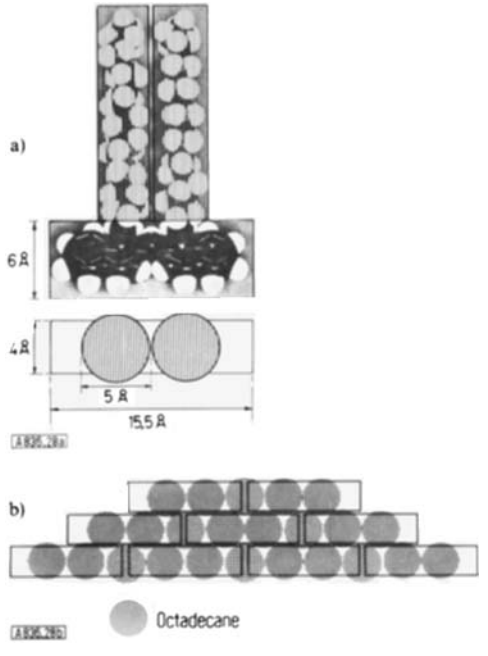


Fig. 28. Structure of Scheibe aggregates (brickwork arrangement). (a) Model of the cyanine molecule *(1)*, views from the side and from above. Chromophore represented as a block and stearyl residues as cylinders. (b) Filling of the gaps between the stearyl residues of the close-packed dye molecules with octadecane gives optimum packing of the stearyl substituents. A mixed layer in the ratio dye: octadecane (1:1) should form Scheibe aggregates particularly well.

A new proposed structure (Fig. 27c, "brickwork" arrangement) gives the correct band shift[34].

One can now try to find a controlled way of producing Scheibe aggregates, even in the case of dyes for which no such aggregates have previously been known[39]. The cyanine molecule *(1)* can be approximately described as a squared block having the dimensions shown in Figure 28a, on which are situated the two cylinders corresponding to the hydrocarbon substituents. It is obvious from this model that close packing of the chromophores is possible only if the paraffin chains are also made to coincide with gaps, *i.e.* the chromophores must be in the brickwork arrangement (Fig. 28b). Such an arrangement is close-packed with regard to the chromophores, but not with regard to the paraffin residues. The layer structure of the hydrocarbon substituents contains a hole large enough for exactly one paraffin chain for each dye molecule. If a mixture of this dye with a long-chain hydrocarbon, *e.g.* octadecane, is spread on a water surface in a molar ratio of 1:1, one would expect a stable mixed layer to be formed, *i.e.* it should be possible in this way to force the formation of Scheibe aggregates. This is in fact found. The typical Scheibe absorption and fluorescence bands are observed (Fig. 29). Table 1 shows that the calculated band shifts of the Scheibe aggregate in relation to the monomer agree well with experiment for several cases.

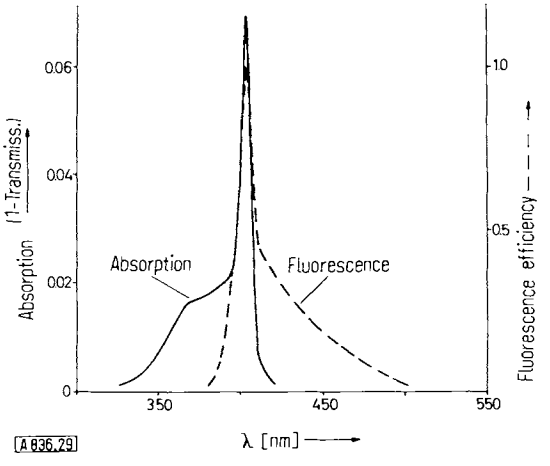


Fig. 29. Absorption and fluorescence spectra of a mixed layer of the dye *(1)* and octadecane in a molar ratio of 1:1. The sharp absorption and fluorescence band at 403 nm is attributable to Scheibe aggregates.

Table 1. Scheibe aggregates of dyes in monomolecular layers. A = aggregate, M = monomer.

Dye	Wavelength of absorption maximum		$\lambda_A - \lambda_M$ (nm)	
	λ_A (nm)	λ_M (nm)	calc.	exp.
(1)	403	388	23	15
(2)	458	432	23	26
(19)	577	533	54	44

When forming the monolayer under usual conditions (increasing the surface pressure to its final value of 30 dyn/cm within less than one minute), the band occurs only in a narrow range of mixing ratios of dye and octadecane of about 1:1. When increasing the surface pressure to its

final value in more than 15 minutes, Scheibe aggregates occur even in pure monolayers of stearyl-substituted cyanine dyes such as *(1)* or *(3)*[40]. Thus the close packing with regard to the paraffin residues as well as the close packing of the chromophores facilitates the formation of the Scheibe aggregates, but is not a necessary condition for their formation.

6. Electrical Phenomena in Layer Systems

6.1. Change in Absorption in an Electric Field

A Scheibe associate monolayer can be incorporated in the usual manner into a system of arachidate layers. The layer system may be prepared on a glass plate with a vacuum-deposited aluminum layer, and covered with a second vacuum-deposited aluminum layer. The result is a capacitor, in which an electric field F of up to 5×10^6 volt/cm can be readily applied to the molecules by application of a potential difference of a few volts[41] (Fig. 30). This leads to a change in the excitation energy $(\Delta E - \Delta E_0)$, *i.e.* a displacement of the absorption band, consisting of a component that depends linearly on F and another component that depends on the square of F:

$$\Delta E - \Delta E_0 = \Delta\mu_y F + \tfrac{1}{2}\Delta\alpha_{yy}F^2 \qquad (9)$$

The shift is given by the changes in the dipole moment $(\Delta\mu_y)$ and in the polarizability $(\Delta\alpha_{yy})$ in the direction of the applied field (y direction). Both components can be easily

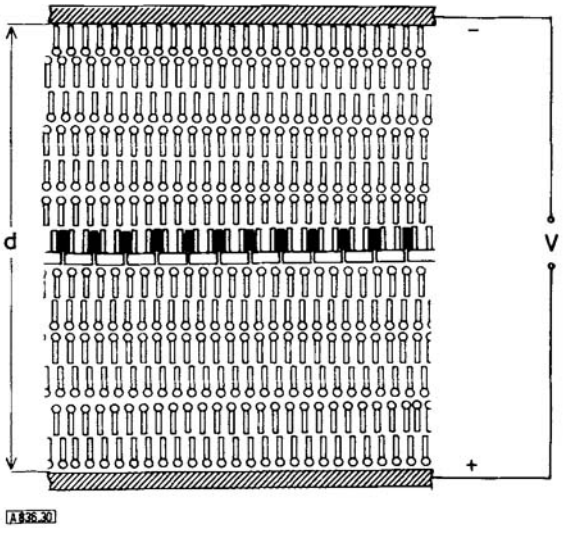


Fig. 30. Investigation of the change in the light absorption of dye molecules on application of an electric field. Layer system with incorporated dye layer between two vacuum-deposited metal layers.

estimated on the basis of the electron-gas model. A consideration in which the branching of the π-electron system is disregarded is sufficient for the first component. The chromophore system then extends over the shaded region in Figure 31a. The wave function of the electron in the highest occupied level has the $1\frac{1}{2}$-cycle wave shown at the bottom left, while on excitation, the electron assumes the two-cycle wave. The points of highest electron density are situated in the antinodes of the wave. It can be seen that on excitation of the molecule, the cloud in the center of the chain is replaced by two clouds underneath, *i.e.* negative charge flows downward in the diagram on excitation, as indicated schematically in Figure 31b.

Thus if the applied field is directed as in Figure 31b, the electron gains energy from the field on excitation, and moves toward the positively charged plate. The absorption band of the individual molecule thus moves toward lower energies on excitation in the field. This results in a corresponding shift of the band of the aggregate; in the classical picture, the equivalent dipole of each dye molecule oscillates more slowly, and the frequency of the coupled in-phase oscillation of these oscillators in the aggregate is also smaller. Reversal of the direction of the applied voltage must lead conversely to a band shift toward higher frequencies. According to this argument, therefore, a linear electrochromic effect is expected, and a value of about +0.2 debye is calculated for $\Delta\mu_y$. The change in polarizability can be determined similarly, and one finds the value $\Delta\alpha_{yy} = +3$ Å^3.

The displacement of the absorption maximum on application of an electric field can be determined experimentally from the change in the absorption. (To obtain simple conditions, the distance between the semitransparent aluminum layers to which the field is applied must be such that the arrangement acts as an interference filter for the measuring light.) One then finds the values $\Delta\mu_y = 0.07$ debye and $\Delta\alpha_{yy} = 1.5$ Å^3, which agree in their signs with expectations ($\Delta\mu_y = 0.2$ debye; $\Delta\alpha_{yy} = 3$ Å^3). In the methods available until now[42], in which molecules are oriented simultaneously by the electric field, it was impossible to separate the dipole moment component from the polarizability component, since both components lead to a quadratic field effect.

6.2. Tunneling of Electrons through Monomolecular Layers

Capacitors consisting of two metal layers and a thin insulating layer can be produced by the monolayer assembling technique. What should happen when a voltage of *e.g.* 1 V is applied to such a capacitor with an insulating layer 30 Å thick? An electron in the metal that hits the potential barrier of the insulator has insufficient energy to overcome this barrier, and it is reflected from the barrier. Because of the wave nature of the electron, however, there is also a certain probability of finding the electron on the other side of the potential barrier, *i.e.* of penetration of the barrier by the electron. This probability is about 10^{-14} in the case of a potential barrier of 1 eV and a barrier thickness of 30 Å, corresponding to an arachidate layer. Thus for every 10^{14} electrons that strike the barrier, only one penetrates. Because of the large number of free electrons in the metal, a measurable current is expected despite the low probability of tunneling. The probability of finding an electron on the other side after it strikes the barrier decreases exponentially with increasing thickness d. Therefore, the same dependence on the barrier thickness is also to be expected for the current.

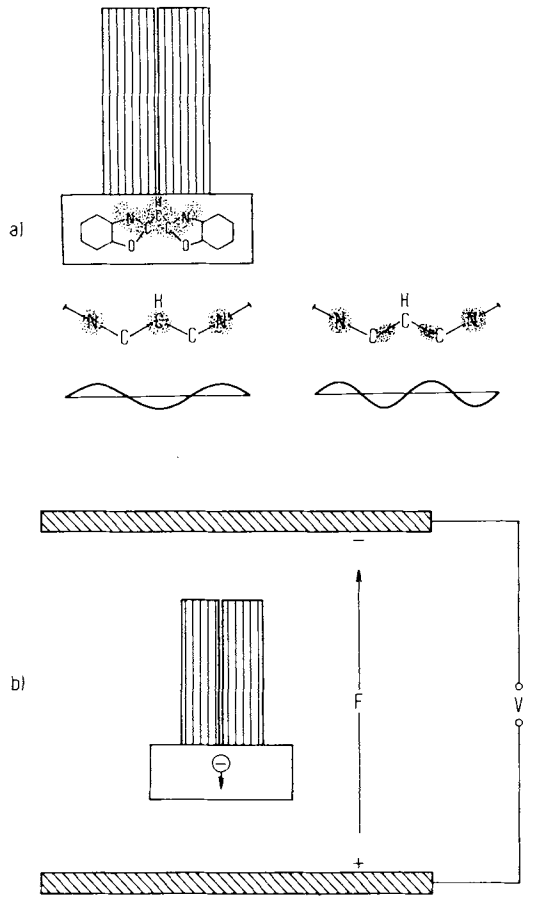


Fig. 31. Change in the excitation energy of a cyanine dye molecule in an electric field. (a) Molecular model showing region of the π-electron system that determines the light absorption. Clouds correspond to the electron wave function in the ground state (left) and in the first excited state (right). The center of gravity of the clouds migrates downward on absorption of light. (b) On absorption of light, negative charge shifts toward the positive electrode. The excitation energy is therefore decreased by the applied electric field.

To determine this dependence experimentally, a monomolecular layer of a fatty acid is first deposited on a microscope slide with a vacuum-deposited aluminum layer. This layer of fatty acid is then covered with mercury or with a vacuum-deposited layer of lead, aluminum, or gold[43, 31]. The tunneling current is in fact found to decrease exponentially with increasing thickness of the fatty acid layer (Fig. 32), and the effects due to the electrode metal (Hg, Al, Pb, Au) can also be quantitatively interpreted.

The excellent agreement between theory and experiment is an extremely sensitive test of the uniformity of the monomolecular layers. Holes or conducting impurities in the layer would strongly influence the electric resistance.

This can be illustrated by an arrangement having an area of 1 cm^2 and a resistance of 1.8×10^7 ohm, *e.g.* in the case of an arachidate layer between an aluminum electrode and a mercury electrode. Let us assume that the fraction $1:10^5$ of the total area exhibits layer imperfections (Fig. 33). Let the distance between the metal electrodes over this small part of the area be slightly reduced, *e.g.* to $\frac{2}{3}d = 18$ Å in the case of an arachidate layer. The properties of the dielectric are assumed to be unchanged. The probability that an electron in the Fermi level will tunnel through the barrier on collision is 10^{-18} for 28 Å and $10^{-18(2/3)} = 10^{-12}$ for 18 Å (Fig. 33). The ratio of the electric current through

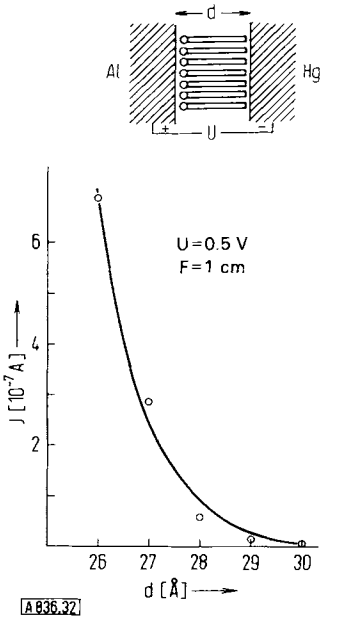


Fig. 32. Experimental investigation of the tunnel effect of electrons. A monomolecular fatty acid layer of thickness d is situated between two metal layers. Current J as a function of d for an area of $F = 1$ cm^2 at an applied voltage of $U = 0.5$ V (Al positive). Circles: experimental values. The curve follows an exponential function.

the layer imperfection to the current through the intact layer in the case considered here is therefore

$$(10^{-12} \times 10^{-5})/10^{-18} = 10$$

The tunneling current due to the imperfection is thus large in relation to the remainder of the current (which agrees with the observed value). This consideration leads to the

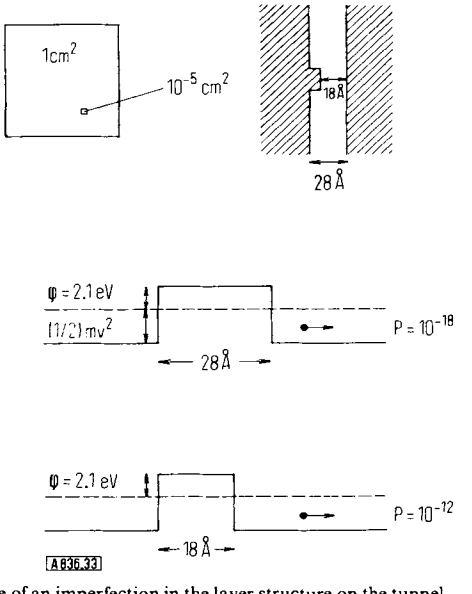


Fig. 33. Influence of an imperfection in the layer structure on the tunneling current. The thickness d of the undisturbed layer is 28 Å. The probability P for tunneling of an electron through the indicated potential barrier is $P = 10^{-18}$, while in the region of the imperfection with $d = 18$ Å, $P = 10^{-12}$. For imperfections amounting to 10^{-5} of the total surface, the tunneling current through the imperfection is ten times that through the intact sample.

conclusion that there is not even such a small proportion of seemingly unimportant layer imperfections.

The negative results of earlier attempts to measure the dependence of the tunneling current on the thickness of the insulating layer in arrangements with monomolecular layers were probably due to this strong sensitivity to imperfections in the layer.

6.3. Photo Current in Monolayer Assemblies

Fig. 34 gives an example of an assembly to investigate the photoconductivity in an organized arrangement[44]. A semitransparent Al layer is coated with several arachidate layers, one monolayer of quinquethienyl *(20)* (mixed layer with arachidate, molar ratio 1:3), and some more layers of arachidate. The second electrode is mercury. The long axes of the quinquethienyl molecules are oriented perpendicular to the layer[44]. A bias voltage U is applied. On illumination of the sample with UV light a photocurrent occurs (rise time less than 2 ms) whose action spectrum agrees with the absorption spectrum of the quinquethienyl layer. The current increases exponentially with increasing voltage U and is proportional to the ratio x/d (x distance between dye monolayer and positive electrode, d distance between the electrodes).

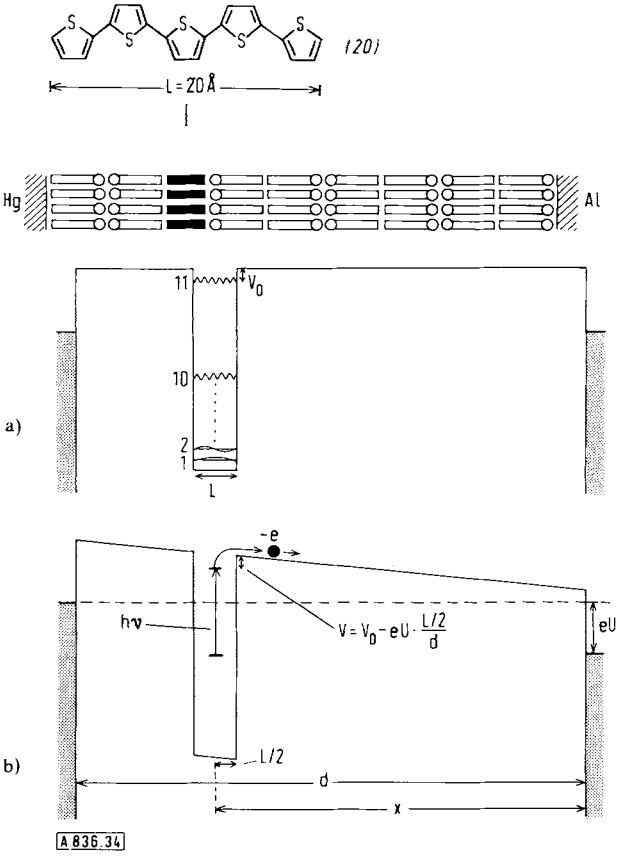


Fig. 34. Photocurrent in monolayer assembly. Monolayer of dye *(20)* between arachidate layers sandwiched between metal electrodes. (a) Potential energy of an electron. Occupied π-electron orbitals 1—10, empty orbital 11. (b) Potential energy when applying a bias voltage U. Energy levels of orbitals 10 and 11. By absorption of light an electron is promoted from orbital 10 to 11 and subsequently lifted to the top of the potential barrier of the arachidate by thermal collisions. Then it moves to the positively biased metal.

When exciting the dye in the arrangement without an applied voltage (Fig. 34a) the electron jumps from the highest occupied to the next orbital and falls back to the ground state, after an average lifetime of the excited state, τ, of about 10^{-11} s. Alternatively, this electron in the excited level of the molecule is thermally excited to the top of the energy barrier of the arachidate and can separate from the dye molecule. When a voltage U is applied to the arrangement, the electron then moves to the positively biased metal (Fig. 34b). The energy barrier between the dye molecule and the positive electrode is diminished by applying the voltage U and according to Fig. 34 this barrier V is

$$V = V_0 - eU\frac{L/2}{d} \tag{10}$$

e is the elementary charge and L the length of the π-electron system. When illuminating the system, n_0 molecules per unit time are excited and n electrons per unit time climb the energy barrier of the arachidate layer. ν_{th} being the frequency of thermal collisions, $\nu_{th}\cdot\tau$ is the number of collisions of the electron during the lifetime of the excited molecule, thus:

$$n = n_0\nu_{th}\tau\exp\left(-\frac{V}{kT}\right) \tag{11}$$

k is Boltzmann's constant and T is the absolute temperature. The current in the external circuit is

$$J = n\cdot e\frac{x}{d} = n_0\nu_{th}\tau e\cdot\frac{x}{d}\cdot\exp\left(-\frac{V_0}{kT}+\frac{eL}{2kTd}U\right) \tag{12}$$

(The charge accumulation in the dye layer is compensated in the dark period in a time large compared with the time of illumination and thus this effect does not influence the photocurrent.)

The observed exponential increase of J with U and the proportionality with x/d is explained by equation (12). By comparison of (12) with the experimental data the value $L = 20$ Å is found, which agrees with the actual length of the molecule. With the known or easily approximated values of the quantities e, n_0, ν_{th}, τ the value $V_0 = 0.4$ eV is obtained. By the tunneling experiments discussed in Section 6.2, $\kappa = 2.2$ eV, where κ is the energy to lift an electron from the top of the arachidate potential barrier up to the vacuum level.

Thus the ionization energy of an electron in the excited level of the dye molecule to vacuum is $I^* = V_0 + \kappa = 2.6$ eV. A value of the order of 3 eV[45] is predicted by theory.

The stearyl-substituted cyanine dyes were prepared by J. Sondermann[46]. *The authors gratefully acknowledge financial support by the Deutsche Forschungsgemeinschaft, the Verband der Chemischen Industrie, and the Adolf-Haeuser-Stiftung.*

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Translation of Genetic Information on the Ribosome[**]

By Gerhard Schreiber[*]

The information for protein structure that is contained in the base sequence of the nucleic acids is translated on the ribosome into the amino acid sequence. This translation can be divided into chain initiation, chain growth, and chain termination. Several specific protein factors and nucleic acids are involved in each section.—For chain initiation, start complexes are formed from the initiating amino acyl-tRNA, mRNA carrying the start signal, and the small and large subunits of a ribosome. GTP and the initiating factors are also involved in this process.—In chain elongation, one amino acid at a time is transferred, in a reaction cycle, from the linkage with tRNA into a linkage with the polypeptide chain. The amino acid to be incorporated is initially bound to the ribosome as amino acyl-tRNA, a process for which GTP and protein factors are necessary. The subsequent formation of a peptide linkage is catalyzed by the peptidyl transferase of the large ribosomal subunit. The peptidyl-tRNA with its newly added amino acid residue is then transferred from the amino acyl-tRNA acceptor site A to the peptidyl donor site P of the ribosome. This requires another protein factor and cleavage of GTP into GDP and phosphate.—Chain termination begins as soon as one of the three terminator triplets UAA, UAG, or UGA in the mRNA reaches the ribosome. The mRNA is moving in relation to the ribosome from the 5' end to the 3' end. Release of the completed polypeptide chain from the ribosome is dependent on release factors. Before initiation of a new polypeptide chain, the ribosomes dissociate into their subunits.

1. Introduction

The amino acid sequence of the proteins of a cell is determined by the base sequence of the deoxyribonucleic acids (DNA) of the cell. The information encoded in the base sequence of the DNA is transformed into the amino acid sequence of proteins in two steps. The base sequence of a DNA is first transcribed into the base sequence of a messenger ribonucleic acid (mRNA). The base sequence of the mRNA is then translated on the ribosome into the amino acid sequence of the protein. The translation process can be broken down into three sections:

1. Initiation of the polypeptide chain.
2. Elongation of the polypeptide chain.
3. Termination of the polypeptide chain.

The reactants that take part in the three sections are shown in Table 1. Details are described below.

Table 1. Reactants in translation.

Reaction	Reactants
Chain initiation	Initiating amino acyl-tRNA Mg^{2+} mRNA (initiation region) Initiation factors (F_1, F_2, F_3) [a] Small and large subunit of ribosome GTP
Chain elongation	Amino acyl-tRNA Mg^{2+}, K^+, or NH_4^+ mRNA Binding factors (T_u and T_s) [a] Factor G (translocase) Ribosome GTP
Chain termination	mRNA (termination region) Release factors (R_1 and R_2) [a] Factor S Dissociation factor Ribosome

[a] The designations for the factors found in *E. coli* are given in parenthesis.

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[**] Based on a lecture delivered in Freiburg on Feb. 3, 1970. The literature is so extensive that a selection has been made here; a more comprehensive list covering publications up to the Spring of 1969 was published by *Lengyel* and *Söll* [1].

2. Initiation

2.1. Reactants

2.1.1. Initiating Amino Acyl-tRNA

Before the amino acids can be used for protein synthesis, they are activated with adenosine triphosphate (ATP) and bound to transfer ribonucleic acid (tRNA). This reaction is catalyzed by amino acyl-tRNA synthetases [eq. (1)]. The initiating amino acid is *N*-formylated methionine in bacteria, chloroplasts, and mitochondria[2–7], and unformylated methionine in eukaryotes[8]. Bacteria[9] and animal cells[8] each contain two methionine-transferring

$$\text{Amino acid} + \text{ATP} + \text{Enzyme} \xrightleftharpoons{Mg^{2+}} \text{Amino acid·AMP·Enzyme} + \text{PP}$$

$$\underline{\text{Amino acid·AMP·Enzyme} + \text{tRNA} \xrightleftharpoons{Mg^{2+}} \text{Amino acyl-tRNA} + \text{Enzyme} + \text{AMP}}$$

$$\text{Amino acid} + \text{ATP} + \text{tRNA} \xrightleftharpoons{Mg^{2+}} \text{Amino acyl-tRNA} + \text{AMP} + \text{PP}$$

$$\Delta G_0' \approx 0$$

$$\text{Enzyme} = \text{Amino acyl-tRNA synthetase} \qquad (1)$$

tRNA species, *i.e.* $tRNA_F^{Met}$ and $tRNA_M^{Met}$ in bacteria, and $tRNA_1^{Met}$ and $tRNA_2^{Met}$ in animals. Only $tRNA_F^{Met}$ and $tRNA_1^{Met}$ transfer methionine for chain initiation. In

bacteria, methionine that is bonded to $tRNA_F^{Met}$ is subsequently formylated to *N*-formylmethionine (fMet)[10]. Met-$tRNA_1^{Met}$, the initiating amino acyl-tRNA in the cytoplasm of the eukaryotes, need not be formylated for chain initiation[8]. $tRNA_M^{Met}$ and $tRNA_2^{Met}$ bind methionine that is to be incorporated into the interior of the polypeptide chain[11].

The specific tRNA for *N*-formylmethionine is characterized by a special arrangement of the complementary bases. Whereas base pairing begins on the fifth nucleotide from the 3'-OH end in the tRNAs transferring amino acids for chain elongation, *e.g.* $tRNA^{Ala}$ from yeast[12], the first complementary base pair in $tRNA_F^{Met}$ occurs in position six[13].

Methionine is formylated only *after* esterification with tRNA (Fig. 1). tRNA cannot bind *N*-formylmethionine[2]. The formyl group is provided by N^{10}-formyltetrahydrofolic acid[10, 14, 15]. The formylating enzyme, Met-tRNA transformylase, has been concentrated more than 1500-fold from *E. coli*[15]. Its molecular weight is only about 25000, and the sedimentation constant is 2.02, *i.e.* the enzyme is of roughly the same size as one of its substrates. X-ray analysis of the $tRNA_F^{Met}$ from *E. coli* with a resolution of 12 Å indicated an elongated molecular shape. According to this analysis, the $tRNA_F^{Met}$ molecule is in the form of a dimer with a length of 109 Å and a thickness of about 35 Å. A single molecule is 80 Å long, and has an irregularly shaped cross section with a "diameter" of 25 to 35 Å[16–18].

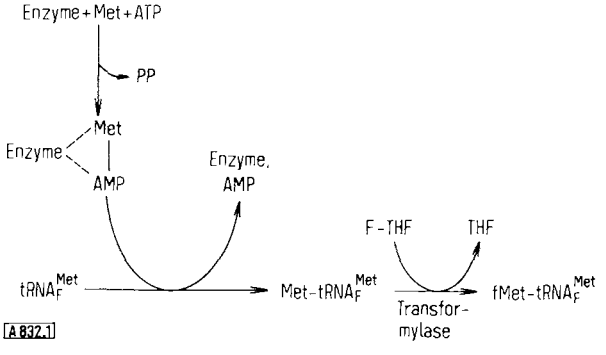


Fig. 1. Activation and formylation of methionine (Met) for chain initiation. THF = tetrahydrofolic acid, F-THF = N^{10}-formyltetrahydrofolic acid, enzyme = methionine-tRNA synthetase.

2.1.2. Mg^{2+} Ions

For a strictly fMet-tRNA-dependent initiation in cell-free systems, the Mg^{2+} concentration must be 4 to 8 mmole/l[19, 20]. Higher Mg^{2+} concentrations lead to nonspecific pseudo-initiations in which the synthesis starts in the middle of a protein instead of at the beginning[21, 22]. However, at high Mg^{2+} concentrations (11 mmole/l), the initiation of the synthesis of a polypeptide still takes place faster with formylmethionyl-$tRNA_F^{Met}$ and AUG (A = adenine, U = uracil, G = guanine) than with other amino acyl-tRNA species and their corresponding codons[23].

2.1.3. mRNA with the Chain Initiation Section

In the mRNA three bases code for each amino acyl-tRNA. The base triplets or codons corresponding to $tRNA_F^{Met}$ and $tRNA_1^{Met}$ are AUG and GUG[8, 9, 24, 25, 122]. The mRNA region providing the start signal for polypeptide chain synthesis must therefore contain the codon AUG or GUG. The mRNA is translated into amino acid sequence from the 5' end to the 3' end[26]. However, neither the triplet AUG nor the triplet GUG was detected among the first 50 nucleotides of the 5' end in bacteriophage RNA[27–30]. Determination of the base sequence of the initiation regions of the RNA of the bacteriophage R 17 showed that the first base of the initiating codon for the coat protein occurs only in position 24, and those for the RNA synthetase and the A-protein (maturation protein) in position 18 of the isolated initiating section[31, 32] (Fig. 2).

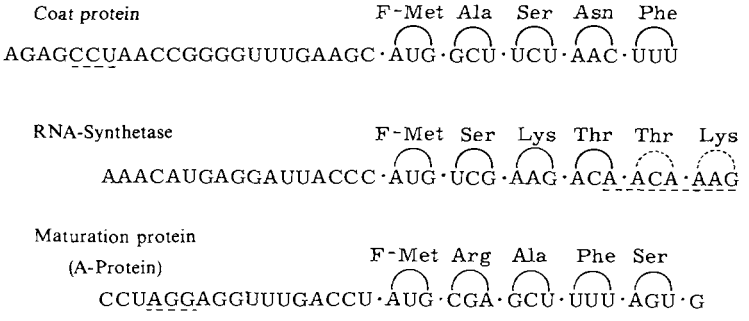


Fig. 2. Base sequence of the three initiating regions of the RNA of the bacteriophage R 17 [31, 32]. Triplets that code for one amino acid are connected by arcs. Sections that have not yet been conclusively verified are indicated by broken lines. Note that the initiating triplet is not situated at the 5' end of the RNA.

Translation of the base sequence of RNA into the amino acid sequence of a protein thus may not begin directly at the 5' end; this conclusion is also supported by the possibility of translation of a cyclic nucleic acid[33, 34]. This may seem surprising at first, but it could be useful for regulation purposes. The RNA region containing the start codon could be held by hydrogen bonds in a double helix in such a way that the initiating codon would be situated in an exposed position at the tip of the helix (Fig. 3)[31, 32]. In

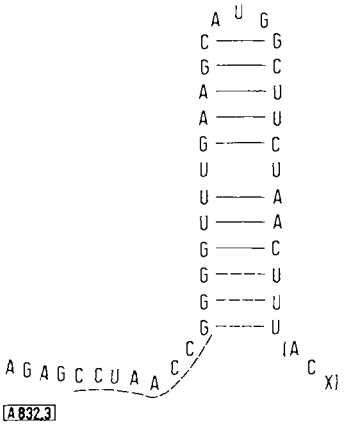


Fig. 3. Exposed position of the initiating codon AUG in the RNA of the bacteriophage R 17 [31, 32]. Sections that have not yet been conclusively verified are indicated by a broken line.

an arrangement like this, the initiating codon would be protected against the action of ribonucleases which attack at the 5' end, and there would also be a possibility of modifying initiation by alteration of the three-dimensional

structure of the RNA. A situation similar to this has been found in the base sequence at the 5′ end of the RNA of the bacteriophage Qβ[35]. Other experiments[36] have shown that the secondary structure of the mRNA does, in fact, play a part in initiation. On modifying the secondary structure of the RNA of bacteriophage f2 by treatment with formaldehyde, additional new starting points occurred along the f2-RNA. This was best explained by assuming that the local rupture of hydrogen bonds leads to changes in conformation of the mRNA, with the result that initiating triplets emerge from the interior to positions that allow initiation.

2.1.4. Initiating Factors

If *E. coli* ribosomes are washed with 0.5 to 2 M NH_4Cl solution, several protein factors that are essential to initiation are released from the 30 S subunit[26, 37–49]. Three factors, F_1, F_2, and F_3, can be separated, and all of these have been purified to homogeneity by analytical electrophoresis on polyacrylamide gel[50–54]. The molecular weight of F_1, which has been crystallized[55], is 9400[50, 55], that of F_2 is 65000—75000[51] or 80000[53], and that of F_3 is 21000 daltons[54, 56]. F_3, a basic protein, is stable to heat treatment and consists of a single polypeptide chain[56]. F_2 and F_3 contain free SH groups[53, 54, 57]. For factor F_3, several variants have recently been described which are specific for the initiation of different proteins[58, 59].

Initiating factors have also been described[60–68] for systems of muscle tissue and reticulocytes. Three factors, M_1, M_2, and M_3, have been distinguished in the reticulocyte system[60]. They are necessary for initiation of the synthesis of the α and β chains of hemoglobin at low Mg^{2+} concentrations and resemble the initiating factors F_1, F_2, and F_3. Only the $tRNA^{Met}$ species that can be formylated are bound to the initiating factors from reticulocytes, while only the $tRNA^{Met}$ species that cannot be formylated are bound to the elongation factors (which will be discussed in Section 3.1.4)[66].

2.1.5. Ribosomes and GTP

Guanosine triphosphate (GTP) and ribosome subunits are also necessary for chain initiation. Structure and composition of the ribosomes are summarized in Table 2. The ribosomes are the supporting framework on which the reactants taking part in the translation fit together in a complicated, 4-dimensional fashion (the fourth dimension being time). In addition to the 80 S-ribosomes in eukaryotes and to the 70 S-ribosomes in prokaryotes, a third class of ribosomes called miniribosomes occurs in mitochondria. They have a sedimentation constant of 55 S (for review see[69]). At least two specific sites on the ribosome have been postulated for binding of amino acyl-tRNA and of peptidyl-tRNA. These two sites, the amino acyl-tRNA acceptor site A and the peptidyl donor site P, can be differentiated by reaction with puromycin. Puromycin, a structural analog of the terminal amino acyl-adenosine portion of an amino acyl-tRNA (Fig. 4)[70], can react with previously formed peptidyl-tRNA[71] to form peptidyl-puromycin and tRNA[72]. However, no further amino acids can be attached to peptidylpuromycin. The result is

Table 2. Properties of the ribosomes and their subunits.

Properties of the ribosomes	Origin: from prokaryotes		from eukaryotes (cytoplasm)	
Particle weight (daltons)	2.8×10^6—3.0×10^6		4×10^6—5×10^6	
Dimensions (Å)	200 × 170 × 170		240 × 200 × 200	
Ratio RNA/protein	1.6—1.8		1	
Sedimentation constants, formation of subunits	70 S → 30 S + 50 S		80 S → 40 S + 60 S	
Properties of the subunits	30 S	50 S	40 S	60 S
Number of protein species per subunit [a]	21	≈40	≈40—50	≈100
RNA of subunits with sedimentation constants [a]	16 S-RNA	23 S-RNA + 5 S-RNA	18 S-RNA	28 S-RNA + 5 S-RNA
Molecular weight of RNA	0.55×10^6	1.1×10^6 and 40000	0.8×10^6	1.7×10^6 and 40000

[a] One molecule of each species per subunit.

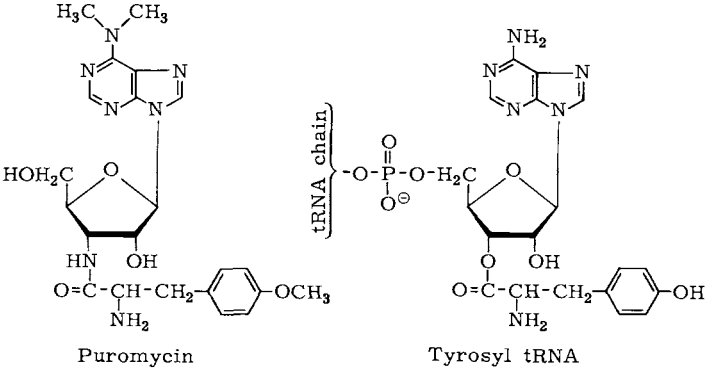


Fig. 4. Puromycin as a structural analog of the terminal amino acyl-adenosine portion of an amino acyl-tRNA.

premature chain termination and the occurrence of peptidylpuromycin and free tRNA[73].

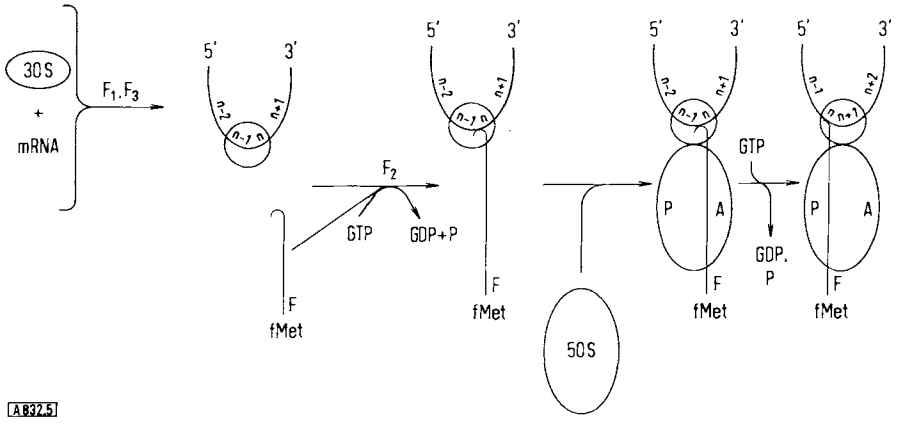
The reaction with puromycin can be used to distinguish between the two different binding sites for tRNA on the ribosome. For example, in a cell-free amino-acid incorporating system programmed with poly-U, polyphenylalanine is formed and initially remains bound to the ribosome as polyphe-tRNA[71]. Two types of peptidyl-tRNA-ribosomes are found in such a system, *i.e.* one type that reacts immediately with puromycin and another that reacts with puromycin only after addition of GTP and of the supernatant obtained on high-speed centrifugation during isolation of ribosomes. It is assumed that ribosomes of the first type have bound the peptidyl-tRNA to the peptidyl donor site P, while those of the second have bound the peptidyl-tRNA to the amino acyl-tRNA acceptor site A. GTP and the supernatant are necessary for the transport of the peptidyl-tRNA from the amino acyl-tRNA acceptor site A to the peptidyl donor site P[73]. During this process, GTP is cleaved into GDP and phosphate. Only then can the peptidyl residue be transferred to puromycin by these peptidyl-tRNA-ribosomes.

Recently, studies using polyribosomes in reticulocytes and muscle cells have shown that two tRNA molecules were bound to one ribosome also *in vivo*, with one of the tRNA molecules carrying a nascent polypeptide chain[74].

2.2. Mechanism of Chain Initiation

A general scheme of chain initiation is shown in Figure 5. fMet-tRNA, the initiating region of a mRNA, and the 30 S subunit of the ribosome, in the presence of GTP and initiating factors, combine to form a complex[25, 46, 54, 75–83]. The initiating region of the mRNA is probably bound to

Opinions differ regarding the precise mode of action of the initiation factors, and particularly as to whether GTP can be replaced by GMPPCP in the binding and liberation of F_1 in the initiation complex[50] or not[99]. There are also various views regarding the sequence of binding and liberation of the start factors in the initiation complexes[50, 54, 90, 100]. It is possible that some of the initiation factors are also involved in chain termination[101]. It has been suggested, for example, that the dissociation factor (see Section 4.1.3) is identical with F_1[102] or F_3[54, 103–105]. Some of the properties of the initiation factors are the same as those of elongation factors[106].



A 832.5

Fig. 5. General scheme of the chain initiation (after *Lengyel* and *Söll* [1], modified). For explanation see text.

the 30 S subunit with the assistance of F_1 and F_3[54], and then fMet-tRNA is added[40, 84]. This step requires the presence of F_2. Only then is the 50 S subunit incorporated[85, 86]. F_3 is necessary only for the binding of natural mRNA[87, 88]. The fMet-tRNA is probably bound first to the amino acyl-tRNA acceptor site A of the ribosome[85, 86, 89–91], but is then transferred to the peptidyl donor site P with cleavage of GTP[41]. In the presence of GMPPCP, a compound analogous to GTP in which the β and γ phosphate groups are joined by a methylene bridge and so cannot undergo enzymatic cleavage[92], a complex fMet-tRNA-mRNA-30 S subunit is formed[76, 82]; the 50 S subunit is then added[85, 89] but no fMet-tRNA-ribosomes that can react with puromycin are made[93]. The fMet-tRNA-ribosomes formed with cleavage of GTP, on the other hand, react with puromycin to give fMet-puromycin, free ribosomes, and tRNA[25, 93–95]. Initial binding of fMet-tRNA to the amino acyl-tRNA acceptor site A is also suggested by inhibition experiments with tetracycline, a compound which was previously found to inhibit specifically binding of other amino acyl-tRNAs to the amino acyl-tRNA acceptor site on the ribosomes[96].

Unlike any other amino acyl-tRNA, fMet-tRNA$_F^{Met}$ cannot form a complex with GTP and the elongation factor T (see Section 3.1.4)[97] from which the amino acyl-tRNA molecules are transferred to the ribosome during elongation of the polypeptide chain. On the other hand, only fMet-tRNA$_F^{Met}$ is bound to 30 S subunits in the presence of initiation factors, GTP, and AUG or GUG. The initiation factors "recognize" both the tRNA portion and the formyl group of the fMet-tRNA$_F^{Met}$[98].

For the regulation of protein synthesis at the level of translation by modifying chain initiation, it is of great interest that factor F_3 could be separated recently into several variants which were specific for the initiation of different proteins[58, 59]. Furthermore, *Dube* and *Rudland* showed that initiation factors isolated from *E. coli* infected with the bacteriophage T 4 reprogrammed ribosomes from uninfected *E. coli* in such a way that these ribosomes preferentially recognized the start signals of T 4-RNA[107]. Protein specificity of the initiation is also shown by experiments using RNA of the bacteriophage R 17. This RNA consists of a single filament with the structural genes for the maturation protein (A protein), the coat protein, and the RNA synthetase, arranged in that order from the 5' end to the 3' end[108]. In a cell-free system from *E. coli* programmed with R 17-RNA, added initiating factors that had been obtained from *E. coli* infected with T 4 resulted in the recognition only of the synthetase-initiating section[109]. In a system from uninfected cells, on the other hand, all three initiating sections of R 17-RNA were recognized, with relative preference for the coat protein.

However, a protein specificity in initiation of the translation may also be due to the source of the 30 S subunit of the ribosomes. In a comparison of cell-free protein-synthesizing systems from *E. coli* and *B. stearothermophilus* which had been programmed with RNA from f2, a bacteriophage related to R 17, it was found that the synthesis of all three phage proteins was initiated with *E. coli* ribosomes, whereas only the maturation protein was initiated in the *B. stearothermophilus* system[110–112]. The specificity for this was located in the 30 S subunits. The source of the

50 S subunit and of the initiation factors was of no importance[110].

A thermally unstable factor that enabled ribosomes from uninfected bacteria to use T 4-RNA selectively as mRNA for protein synthesis has been isolated from *E. coli* infected with T 4[113].

The above description is valid for chain initiation in prokaryotes, mitochondria, and chloroplasts. In eukaryotes, unformylated Met-tRNA[8], which could however be formylated by a transformylase isolated from *E. coli*[114-117], was found to be the initiating amino acyl-tRNA. The cytoplasm of liver and yeast cells contains no transformylase.

As the initiating amino acid for globin, methionine is split off at an early stage[118, 119] when the growing polypeptide chain of globin has reached a chain length of 15 to 20 amino acids. Methionine has also been identified as the initiating amino acid for protamine in cell suspensions from trout testes[120]. Enzymatic removal of methionine from the next amino acid, proline, has been detected but probably occurs only after formation of protamine is complete. In *N. crassa*, another eukaryotic organism, though no methionine can be detected as the N-terminal amino acid of completed cell proteins, ^{14}C-methionine is found near the N-terminal end in nascent proteins[121].

The initiating tRNA from eukaryotes can be used as initiating tRNA in cell-free systems prepared from *E. coli*[4, 5, 114-117]. $tRNA_1^{Met}$ is probably the only initiating tRNA in eukaryotes[122]. In view of the rapid formation of methionylpuromycin with Met-$tRNA_1^{Met}$ from liver, it was proposed that Met-$tRNA_1^{Met}$ is bound to the peptidyl donor site P of the ribosome[115].

Initiating factors in systems from mammals have already been discussed in Section 2.1.4. Protein specificity or organ specificity of the initiating factors has also been described for eukaryotes. The factors from reticulocytes and from muscle mainly stimulate the synthesis of globin and of myosin, respectively[64].

3. Chain Elongation

3.1. Reactants

3.1.1. Amino Acyl-tRNA

Most of the amino acids occurring in proteins can be bound to more than one tRNA species. However, there is probably only one activating enzyme for each amino acid[1, 123-125] [eq. (1)]. The specificity of the transfer of the amino acids to one of the appropriate tRNAs is greater than the specificity of the reaction of the amino acid with the enzyme and with ATP[123-127]. For example, Ile-tRNA synthetase also activates valine, and Val-tRNA synthetase also activates threonine, but these "wrong" amino acids are not then transferred to the corresponding tRNA[128-130].

Since the base sequences of a number of tRNAs have now been established, it is possible to deduce the general structural principle of the tRNAs[18, 131]. All tRNAs can be written in "clover-leaf" form with five arms (Fig. 6): the amino acid arm or stem, the dihydrouridine arm (DHU arm), the anticodon arm, and the thymine-pseudouridine-cytosine arm (TΨC arm). The tRNAs can be divided into

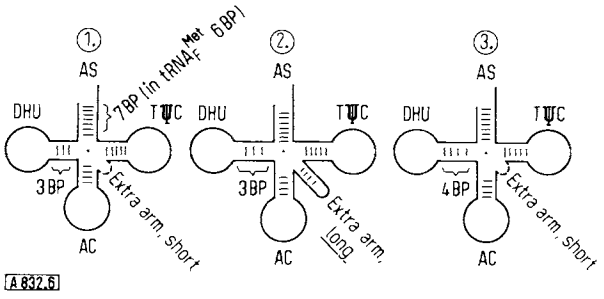


Fig. 6. Grouping of the tRNAs into three classes (after *Staehelin* [131], modified). BP = base pairs, AS = amino acid arm, DHU = dihydrouridine arm, AC = anticodon arm, TΨC = thymine-pseudouridine-cytosine arm.

three classes according to the structure of these arms; the tRNAs of class 1 have three base pairs in the DHU arm and a short extra arm, those of class 2 also have three base pairs in the DHU arm, but a long extra arm, and those of class 3 have four base pairs in the DHU arm and a short extra arm (Fig. 6). Comparison of the base sequence of "normal" wild type tRNA with that of tRNA that has been functionally modified by mutation should provide information about the functional importance of the various tRNA regions. A number of tRNAs have been crystallized,

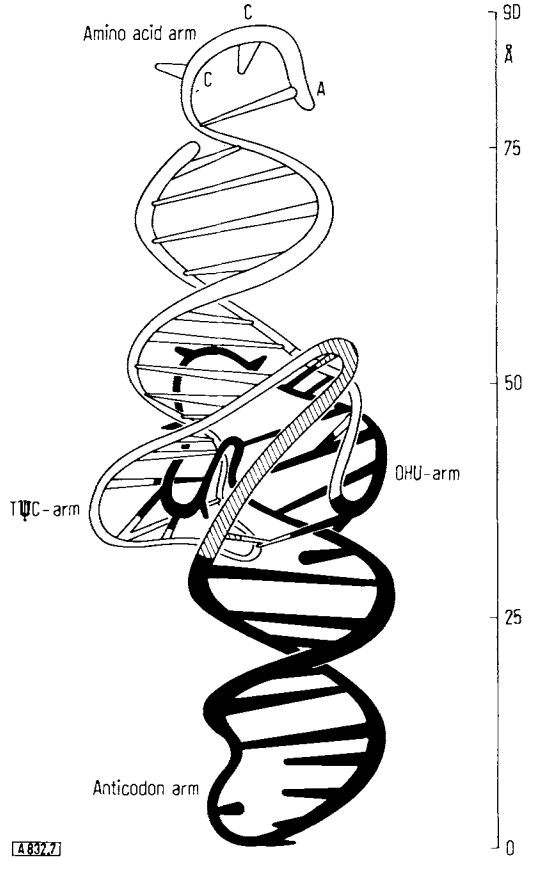


Fig. 7. Model of the three-dimensional structure of $tRNA_F^{Met}$ after *Levitt* [18]. ■: DHU and anticodon arms; □: TΨC and amino acid arms; ▨: extra arm.

with the result that X-ray analyses are now possible[16, 17, 132–140]. On the basis of the data obtained, for example, the three-dimensional tRNA model shown in Figure 7 has been proposed[18].

3.1.2. Mg^{2+}, K^+, or NH_4^+ Ions

Unlike proper chain initiation, elongation can take place at low (4—8 mmole/l) and at high (>10 mmole/l) Mg^{2+} concentrations. At $[Mg^{2+}]>10$ mmole/l, amino acyl-tRNAs are probably bound both to the amino acyl-tRNA acceptor site *and* to the peptidyl donor site of the ribosome. Amino acids are thus incorporated from amino acyl-tRNA into polypeptidyl-tRNA without the need for initiating amino acyl-tRNA or initiating factors[19, 141, 142]. The presence of K^+ or NH_4^+ is necessary for chain elongation[143, 144].

3.1.3. mRNA

Heteropolymeric or homopolymeric polyribonucleotides can be used in cell-free systems as "synthetic" mRNAs. The stimulation of the incorporation of phenylalanine into polyphenylalanine by poly-U, for example, has been studied extensively[145]. The RNA of bacteriophages is often used as "natural" mRNA in cell-free systems. The mRNA of microorganisms is generally polycistronic[146], *i.e.* it contains the structural information for several proteins. The RNA of the bacteriophage R 17 consists of a nucleic acid filament containing the information for the amino acid sequence of the three phage proteins[108]. Arranged sequentially from the 5′-phosphate end to the 3′-OH end, these proteins are: the maturation or A protein (350 amino acids[147]); the coat protein (129 amino acids[148, 149]); and the RNA synthetase (450 amino acids[150]). The nucleotide sequence of the RNA of the bacteriophage f2 differs only slightly from that of the bacteriophage R 17 in the region of the coat protein cistron[151]. Eukaryotic mRNA appears to be monocistronic[152].

3.1.4. Elongation Factors

Protein factors for chain elongation were first isolated from the supernatant obtained by high-speed centrifugation of *E. coli* extracts. Two factors, G and T, were distinguished[153, 154] which could be crystallized[155, 156]. The factor G has a molecular weight of 84000, and dissociates in 4 M urea solution into two subunits with molecular weights of 42550 each, and in 8 M urea solution into a total of four inactive subunits, each of which is reported to have a molecular weight of 23260. Reagents which react with sulfhydryl groups inhibit the activity of factor G[157, 158]. In rapidly growing *E. coli*, the translocase (=factor G) constitutes 2% of the total protein of the ribosome-free extract[159]. The T factors from *E. coli* and from *P. fluorescens* have been resolved into a thermally more stable component T_s and a thermally less stable component T_u[160]. The factor T_u and the factor T_s combine to form a complex which decomposes in the presence of GTP into a T_u-GTP complex and T_s[161].

The three elongation factors S_1, S_2, and S_3 obtained from *B. stearothermophilus* correspond to the factors T_s, G, and T_u. However, they are all relatively stable to heat[162]. Elongation factors have also been isolated from yeast[163, 164]. The elongation factors found in rat liver[165] were later resolved into two fractions named transferase I and transferase II[166, 167]. In their mode of action they correspond to the factors T and G[168–175]. The molecular weight of transferase I is 186000, and that of transferase II is 70000[176]. Transferase II contains SH groups essential for activity[176]. Transferase I is also known as binding enzyme, and transferase II as translocase.

Only one factor T and one factor G have been detected in prokaryotes[177], whereas two or more types of binding enzymes or translocases have been isolated from eukaryotes[177–180]. Of these, it is possible that one type is specific for 70S ribosomes and another for 80S ribosomes[177, 178, 181]. It has also been reported, however, that exchange of the elongation factors between cell-free systems from prokaryotes and from eukaryotes is possible[182, 183] without interfering with the incorporation of amino acids into proteins. Moreover, it is not yet known whether organ specificity occurs for the elongation factors[184, 185]. A mutant of *E. coli* that was resistant to fusidic acid, a specific inhibitor of the translocation (see Section 3.2), was recently reported. This mutant had a modified G factor[186].

3.1.5. Ribosomes and GTP

GTP is necessary both for binding of the amino acyl-tRNA and for translocation of newly formed peptidyl-tRNA from the amino acyl-tRNA acceptor site A to the peptidyl donor site P.

The properties of the ribosomes were described in Section 2.1.5 and in Table 2. It has been suggested that the large subunit of the ribosomes from rat liver has a tunnel or channel through which the proteins pass that are to be transported into the intracisternal space of the endoplasmic reticulum[187, 188]. The ribosome is situated with the large subunit toward the endoplasmic membrane[189, 190].

3.2. Mechanism of Chain Elongation

A general picture is shown in Figure 8. The following description is based mainly on experiments with cell-free systems incorporating amino acids into protein-like material. A complex is first formed from amino acyl-tRNA, the factor T_u, and GTP[162, 191]. Uncharged tRNA (=tRNA carrying no amino acid) is not bound and does not inhibit the binding of amino acyl-tRNA[97, 162, 192]. The amino acyl-tRNA is transferred from the complex to the amino acyl-tRNA acceptor site A on the ribosome. After binding of the amino acyl-tRNA to the mRNA-ribosome complex, GTP is broken down[193]. This cleavage of GTP appears to occur before the formation of the peptide linkage and before translocation, since fusidic acid, an antibiotic that inhibits GTPase activity of the protein factor G, which is involved in the translocation, does not inhibit cleavage of GTP by T_u+T_s[193]. In the presence of GMPPCP, which cannot be broken down enzymatically into GDP

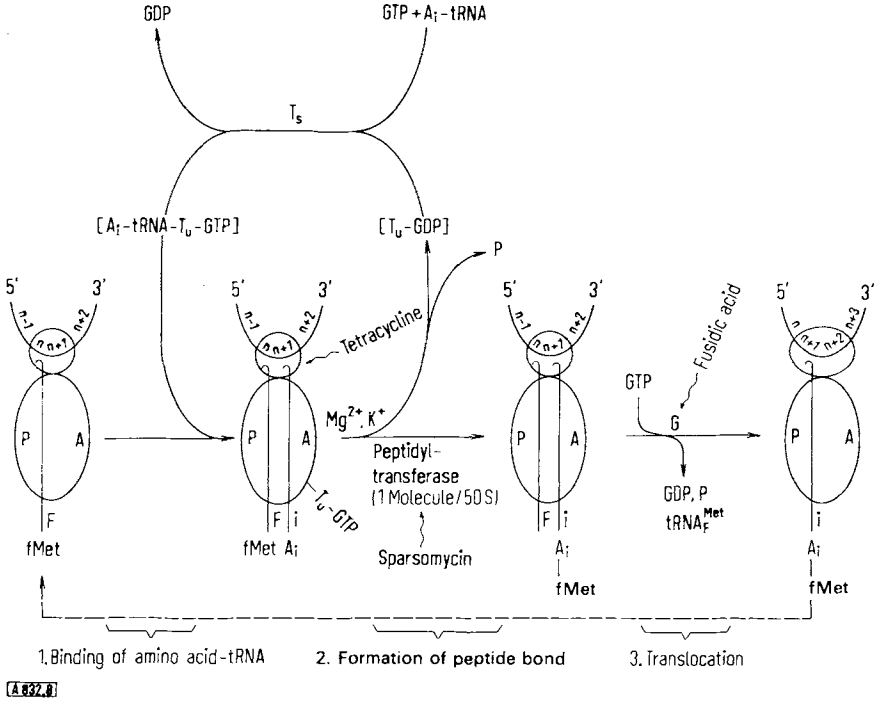
and phosphate, the amino acyl-tRNA is still bound to the mRNA-ribosome complex, but no peptide linkage is formed, in contrast with the observations with GTP[193–195].

Sparsomycin, an antibiotic that inhibits the formation of the peptide linkage[196, 197], affects neither the binding of amino acyl-tRNA to the ribosome[198] nor the cleavage of GTP by $T_u + T_s$[193]. The factor T_s probably has the function of regenerating amino acyl-tRNA-T_u-GTP from GTP, amino acyl-tRNA, and the complex T_u-GDP which is liberated after binding of the amino acyl-tRNA to the ribosome[199]. The same T_u factor can react with several amino acyl-tRNA species[97].

The first observations on the cleavage of GTP during binding of amino acyl-tRNA to the mRNA-ribosome complex and on the need for a supernatant factor were made with cell-free systems from reticulocytes[200].

tRNA acceptor site, play a part in the reaction with peptidyl transferase[207, 208]. The peptidyl transferase in bacteria appears to catalyze only the reaction of amino acyl-tRNA with a blocked α-amino group. This may be the reason why the amino group of methionine must be formylated in the initiating amino acyl-tRNA in bacteria. During chain elongation, the blocking group is the peptidyl residue. It is possible that, in the course of evolution, a different mechanism has developed in the larger ribosomes from eukaryotes, with the result that specificity of initiation is guaranteed even with an unformylated initiating amino acid.

The newly formed fMet-amino acyl-tRNA is then transferred from the amino acyl-tRNA acceptor site A to the peptidyl donor site P, and the now uncharged $tRNA_F^{Met}$ is released from the peptidyl donor site. The ribosome on the mRNA moves by one triplet in the 5′→3′ direction[209].



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Fig. 8. General scheme of the chain elongation (after *Waterson, Beaud* and *Lengyel* [199], modified). A_i = amino acid. For further explanations, see text.

After the binding of the new amino acyl-tRNA to the amino acyl-tRNA acceptor site A, formylmethionine is released from its linkage with $tRNA_F^{Met}$ and is then transferred to the α-amino group of the new amino acyl-tRNA, resulting in formation of a peptide linkage. The fMet-amino acyl-tRNA is still bound to the amino acyl-tRNA acceptor site of the ribosome[194, 201, 202]. The enzyme that catalyzes the reaction, *i.e.* the peptidyl transferase, is a structural protein of the 50S subunit of the ribosome[3, 73, 203, 204]. A 50S subunit contains exactly one molecule of peptidyl transferase[205]. Neither proteins from the supernatant obtained on high-speed centrifugation nor GTP are involved directly in the reaction[3, 203, 204, 206]. However, Mg^{2+} and K^+ or NH_4^+ ions are necessary[143, 144]. The 3′-terminal CCA ends of the tRNA, both in the peptidyl-tRNA bound to the peptidyl donor site and in the amino acyl-tRNA bound to the amino acyl-

The translocation in the cell-free system depends on the presence of the protein factor G and the cleavage of GTP into GDP and phosphate[194, 201, 202, 210–212]. The amino acyl-tRNA coded by the next triplet of the mRNA can now take its place on the vacated amino acyl-tRNA acceptor site of the ribosome, and the cycle can start again.

Like the cleavage of GTP, the translocation is blocked by fusidic acid[211, 212]. Mutants of *E. coli* that are resistant to fusidic acid have a modified G factor[213]. The translocation is also inhibited by GMPPCP[92, 194, 202, 210, 211].

In systems from rat liver, the functions of transferases I and II[165–167] are essentially the same as those of the factors T and G, respectively[168–175]. A single molecule of transferase II can catalyze the translocation on several ribosomes[175]. Transferase II is specifically inactivated by diphtheria toxin[214, 215].

4. Chain Termination

4.1. Reactants

4.1.1. mRNA with the Termination Region

The termination signals in the mRNA are the triplets UAA, UAG, and UGA[216-226]. These are known as ocher, amber, and opal codons, respectively. Since they stimulate neither the binding of one of the known amino acyl-tRNAs to ribosomes[227,228] nor the incorporation of amino acids into protein-like material[229], they have also been called nonsense codons. It was assumed that terminator triplets could immediately succeed one another[230], and this was recently confirmed by the elucidation of the base sequence of the region containing the termination signal of the RNA from bacteriophage R 17[231]. It remains to be seen whether double termination signals generally occur. This would provide protection against the synthesis of nonsensical proteins as a result of mutation of the termination signal, and would thus offer a selection advantage to the organism in question.

4.1.2. Release Factors

The presence of a release factor[232] is necessary for the release of the completed polypeptide chain from the polypeptidyl-tRNA-ribosome complex. Two types of release factors, R_1 and R_2, have been distinguished. R_1 is specific for UAA and UAG, and R_2 is specific for UAA and UGA[233,234]. The factors are present in the cytoplasm, are not dialyzable, and are inactivated by trypsin and *N*-ethylmaleimide, but not by ribonuclease[234]. These properties correspond to those of proteins containing free sulfhydryl groups. The molecular weight of R_1 is 44000, and that of R_2 is 47000. One bacterium is thought to contain about 500 molecules each of R_1 and R_2[235]. With 30000 ribosomes per bacterium[236], this would correspond to one release factor per 30 ribosomes.

The recognition of the terminator triplet is assisted by another protein, the factor S[237].

4.1.3. Dissociation Factor and Ribosomes

After release of the polypeptidyl-tRNA, the mRNA-ribosome complex dissociates[238,239]. The ribosomes are released either directly as subunits or as free 70S-ribosomes[240-243], which then dissociate into subunits. This process involves the action of the dissociation factor[244]. Like the initiating factors, this has been found on the native 30S subunits, but not on 70S ribosomes. However, it appears to be bound to the ribosome before the dissociation begins[245]. The dissociation factor remains on the small subunit after the cleavage of the ribosomes. It is possible that free 70S ribosomes in the cell or in the bacterium are an artefact[246]. The dissociative action of the initiating factors was mentioned in Section 2.2. The dissociation factor may be identical with F_3[54,55,103,105]. In *E. coli*, F_3 is the only dissociation factor[104].

The dissociation factor may be species-specific, since a protein fraction from *Saccharomyces cerevisiae* that exhibited dissociative activity towards ribosomes from *Saccharomyces* had no dissociative action on ribosomes from *Escherichia coli* or from rabbit reticulocytes[247].

4.2. Mechanism of Chain Termination

As soon as one or two of the terminator codons have reached their amino acyl-tRNA acceptor sites in the movement of the mRNA along the 30S subunit, the polypeptide chain synthesis stops[216,218-220]. If a nonsense codon is formed by mutation from a triplet coding for an amino acid, the result is premature chain termination and the synthesis of a protein fragment[248].

The investigations on chain termination were carried out mainly on mutants of the phages R 17 and f2 with a UAG triplet formed by mutation. Phages in which this triplet was formed at the beginning of the gene for the coat protein were used, and the synthesis of a hexapeptide corresponding to the N-terminal end of the coat protein was observed in cell-free systems[232,249,250]. The hexapeptidyl-tRNA formed was still bound to the mRNA-ribosome complex, and could thus be used as a substrate (Fig. 9) for the detection of the release factor. Another test substrate was the AUG-fMet-tRNA-ribosome complex

1. Hexapeptidyl-$tRNA_6$-ribosome-RNA
2. fMet-$tRNA_F^{Met}$-ribosome-AUG

Fig. 9. Substrates for the detection of the release factor.

formed on incubation of AUG with fMet-tRNA and ribosomes. Formylmethionine was liberated from this complex in the presence of release factors and one of the nonsense triplets[233]. Using these tests, two release factors R_1 and R_2 having the codon specificity described in Section 4.1.2 were isolated[234,235]. It has recently been shown that R_1 and R_2 are necessary not only for the release of incomplete, short oligopeptide fragments but also for the release of completed proteins[251,252].

Formylmethionine is liberated only when formylmethionine-tRNA is bound in the peptidyl donor site P, suggesting that polypeptides are released from the peptidyl donor site. The liberation is inhibited by sparsomycin, chloramphenicol, and other antibiotics[253].

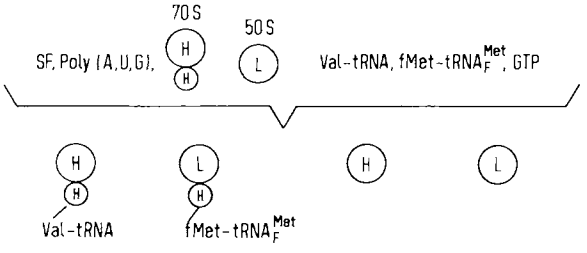
Experiments with a puromycin analog in which the α-amino group had been replaced by a hydroxyl group were recently described[254,255]. The peptidyl transferase was able to transfer the peptidyl residue to the hydroxyl group of the puromycin analog. However, this process was slower than the formation of the peptide linkage. In other experiments, formylmethionine ethyl ester was liberated by nucleophilic attack of ethanol on fMet-$tRNA_F^{Met}$ on the ribosome[256]. The reaction was stimulated up to 20-fold by tRNA or the codon CCA. This raises the question whether the specificity of the peptidyl transferase is modified in chain termination, with the result that the polypeptidyl residue is transferred to a hydroxyl group, *e.g.* of water, instead of to another amino acid. Binding experiments indicate that R_1 and R_2 could be important in the recognition of the terminating codon[253,257], in which the protein factor S has a stimulating effect[237].

Before the formation of a new initiating complex, the ribosomes must dissociate into subunits. The dissociation factor takes part in this dissociation, not as a catalyst, but

in the stoichiometric quantity with respect to the ribosomes[244]. The dissociation of the ribosomes into subunits before the start of the synthesis of a new polypeptide chain was shown by exchange experiments, in which a growing bacterial culture was transferred from a medium containing heavy isotopes into one containing light isotopes[258, 259].

The dissociation of the ribosomes before the binding of the initiating amino acyl-tRNA has also been demonstrated in cell-free systems. "Heavy" 70S ribosomes were obtained from *E. coli* that had been grown in a medium containing D_2O and ^{15}N. "Light" ribosome subunits were isolated from *E. coli* that had been grown in a medium containing H_2O and ^{14}N. "Heavy" 70S ribosomes were then incubated with "light" 50S subunits, poly(A,U,G), initiating factors, Val-tRNA, fMet-$tRNA_F^{Met}$, and GTP under conditions suitable for the synthesis of protein. The mixture was then analyzed by centrifugation in a density gradient. It was found that fMet-$tRNA_F^{Met}$ was bound mainly to hybrid light/heavy ribosomes, whereas Val-tRNA occurred mainly on pure heavy/heavy ribosomes. Free heavy and light subunits were also found.

The experiment is illustrated schematically in Figure 10. It follows that the ribosomes must dissociate into their



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Fig. 10. Dissociation of the ribosomes before the initiation of a new polypeptide chain (schematic). H and L denote the use of D_2O and ^{15}N and of H_2O and ^{14}N, respectively, in the medium in which the bacteria were grown and from which ribosomes or ribosomal subunits were isolated. The bracket symbolizes the incubation for the protein synthesis. SF = initiating factors. For further explanations see text.

subunits before the binding of fMet-tRNA required for chain initiation can occur. However, Val-tRNA required for the chain elongation can be bound without dissociation of the ribosomes[77]. Dissociation of ribosomes and the exchange of ribosomal subunits were also detected for eukaryotes[260–265].

When the rate of protein synthesis decreases, 70S ribosomes accumulate. To explain this, it was suggested[246] that ribosomes are normally released from mRNA as subunits. When protein synthesis decreases, subunits accumulate, and can combine to form 70S ribosomes. However, these 70S ribosomes cannot take part in protein biosynthesis. They may be regarded as a sort of pool of subunits that are not required for the time being, but which are remobilized when protein synthesis increases again.

5. Rate of Translation

A survey of the rates found for elongation of the polypeptide chain is presented in Table 3. It can be seen that elongation proceeds only very slowly in cell-free systems. The highest

Table 3. Time required for the elongation of the polypeptide chain.

System	Amino acid/second	T (°C)	Ref.
Viruses			
TMV protein; *in vivo*;	>2—3	15	[266]
(in leaf sections)	>20	28	
f2 phage coat protein; cell-free system from *E. coli*	0.4—0.5	32—33	[239]
T4-phage lysozyme; cell-free system from *E. coli*	1.6	25	[267]
	3.0	31	
Bacteria			
Anthranilic acid and tryptophan synthetase in *E. coli*	6.9±1.4	37	[268]
Maximum and 30% maximum induced β-galactosidase in *E. coli*	15	37	[269]
β-Galactosidase (at start of induction) in *E. coli*	13.0—14.6	37	[270]
Eukaryotes			
Hemoglobin in rabbit	0.5	15	[271]
reticulocytes	2	37	
Egg white lysozyme in homogenized chicken oviduct tissue	1	37	[272]
Albumin in perfused rat liver	3.7—4.6	not reported	[273]
Globin β chain in rabbit	2—3	30	[274]
reticulocytes	4—6	37	
Hemoglobin in chicken erythrocytes	2.5	37	[275]
Globin α chain in rabbit	0.83	20	[276]
reticulocytes	8.3	37	
Globin β chain in rabbit	0.58	20	
reticulocytes	5.2	37	

rates were found for the synthesis of virus protein in tobacco leaves[266] and for the synthesis of β-galactosidase in *E. coli*[269]. The rate of elongation of the polypeptide chain was the same for maximum induction and for only 30% of the maximum induction of β-galactosidase. In hemoglobin, the α chain of the globin is elongated more rapidly than the β chain[276]. The observed rates depend on the temperature. However, the poikilothermic toad-fish *(Opsanus tau)*, an organism which can adapt itself to low water temperatures, manages to maintain a constant elongation rate even at low temperatures[277]. The period of the ribosome cycle, *i.e.* polypeptide chain synthesis + dissociation + reassociation of the subunits, has been found to be 10 minutes at 37 °C in *B. licheniformis*[278] and 7—10 minutes in *B. megaterium*[279]. These values are in agreement with the measured elongation rates if it is assumed that one ribosome translates one polycistronic mRNA filament *in vivo*.

6. Energy Requirement of Protein Synthesis

The activation of the amino acids requires two ATP per amino acid. In *in vitro* experiments in which the factor G was incubated with the amino acyl-tRNA-GTP-T_u complex, it was found that cleavage of GTP, which plays a part in the binding of the amino acyl-tRNA to the mRNA-ribosome, does not allow subsequent translocation. This means that, at least *in vitro*, a quantity of energy equivalent to four ATP is required per amino acid incorporated.

7. Cell-Free Synthesis of Specific Proteins

The mechanism of translation can be studied in cell-free systems performing only some parts of translation. For example, such systems may be able to elongate previously started polypeptide chains, but may not be able to initiate new chains. To investigate the regulation of the synthesis of specific proteins *in vitro*, the complete *de novo* synthesis in a cell-free system is necessary.

The complete *de novo* synthesis of specific proteins in cell-free systems has been described repeatedly (for review of the literature see *Nisman* and *Pelmont*[280]). As long ago as 1962 the *de novo* synthesis of β-galactosidase and of alkaline phosphatase in cell-free preparations of *E. coli* had been reported[281]. When those experiments were repeated under the conditions described for isolation and incubation[281, 282], it was found, however, that the so-called cell-free preparations still contained viable cells, and that the observed synthesis of β-galactosidase could probably be entirely accounted for by those viable cells[283]. Adequate checks for presence of bacteria are missing in many of the published cell-free syntheses of specific proteins in systems from microorganisms.

In recent years, stimulation of the synthesis of viral proteins in cell-free systems from *E. coli* by virus nucleic acids has also been studied. Cell-free synthesis of α- and β-glucosyltransferase[284–286], lysozyme[285, 287–290], d-CMP-deaminase[285] and β-galactosidase[291] in systems from *E. coli* programmed with bacteriophage DNA have been described. The amount of lysozyme synthesized *in vitro*[288] was, however, only 0.1—1% of that made *in vivo*[292]. Finally, cell-free synthesis of monomers of alkaline phosphatase[293] and tryptophanase[294] in systems from *E. coli* may be possible. Also, *in vitro* syntheses of proteins of animal viruses, *e.g.* poliovirus[295] and SV 40-virus[296], in cell-free systems from *E. coli* containing poliovirus-RNA or SV 40-DNA have been published.

Besides contamination by intact cells, which presents special problems in cell-free systems from prokaryotes to which no inhibitors of bacterial protein synthesis can be added, a careful characterization of the product of the reaction is imperative. For cell-free systems incorporating labeled amino acids into the globin part of hemoglobin, for example, considerable amounts of labeled amino acids were found to be incorporated into peptides not belonging to hemoglobin[297]. If cell-free *de novo* synthesis of specific proteins is demonstrated only by incorporation of radioactive amino acids, proteins have to be purified to constant specific radioactivity. Many of the earlier reports on the cell-free synthesis of albumin, in which radioactively labeled albumin was isolated by immunoprecipitation[298–320], have to be reevaluated since immunoprecipitation either on cellulose as supporting material[321, 322] or in solution[323] has been shown not to yield radiochemically pure albumin[323–325]. In a cell-free system from rat liver effectively incorporating ^{14}C-leucine into trichloroacetic acid-precipitable material, no *de novo* synthesis of albumin could be demonstrated if albumin was purified to constant specific radioactivity[326]. Finally, amino acids may be bound to proteins by mechanisms other than protein biosynthesis and thus may simulate incorporation by protein biosynthesis. This possibility is discussed elsewhere in detail[325–327].

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COMMUNICATIONS

Cyclopropanimines. A Novel Variant of the Favorskii Reaction[**]

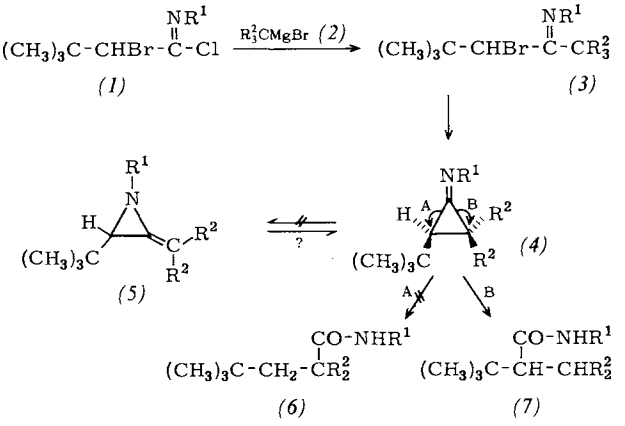
By *Helmut Quast, Edeltraud Schmitt*, and *Rolf Frank*[*]

Whereas the thermal valence isomerization of several hetero methylenecyclopropanes has been established[1], the interconversion of methyleneaziridines and cyclopropanimines is still a matter of speculation[2, 3], not least because cyclopropanimines have repeatedly defied attempts at preparation[4]. We now report the first synthesis of a cyclopropanimine and a novel variant of the Favorskii reaction. Since this rearrangement of α-halo ketones is known to occur *via* cyclopropanones[5, 6], a 1,3-elimination starting from the (previously unknown) α′-unsubstituted α-halo ketimines of type *(3)* seemed an attractive approach to cyclopropanimines, which have only been postulated as intermediates so far[2, 3, 6, 7].

Treatment of the imidoyl chlorides *(1a)*—*(1d)*, readily available from the corresponding amides and an excess of thionyl chloride, with the Grignard compound *(2)* in ether at low temperature afforded the imines *(3a)*—*(3d)* in high yield. Potassium *tert*-butoxide in tetrahydrofuran converted *(3a)* and *(3b)* into *(4a)* and *(4b)* (b. p. 20—22 °C/10^{-3} torr) in 93—96% yield. *(3c)* and *(3d)* gave the same reaction, as shown by the IR spectra of the reaction mixtures.

The cyclopropanimine structure *(4a)* and *(4b)* was assigned on the basis of elemental analysis, base equivalent weight, IR, NMR, and mass spectra. *(4a)*, IR[8]: 3050 (CH_2), 1773 (C=N), 973, 1013, 1031 cm^{-1} (cyclopropane ring). The NMR spectrum[8] shows the signals of R^1 at 0.73—0.91 (12 H/m), 1.75—2.91 (2 H/m), and 2.61 ppm ($J = 6.0$ Hz, 1 H/t), a *tert*-butyl singlet at 0.96 ppm, and a multiplet of the ring protons at 0.9—1.7 ppm. The mass spectrum displays a weak molecular ion and fragments of composition $M-CH_3$, $M-C_3H_7$, $M-C_4H_9$, and R^1 (50%). *(4b)*, IR[8]: 2295 (CD_2), 940, 977, 1043, 1064 cm^{-1} (cyclopropane ring). NMR[8]: The multiplet of the ring protons of *(4a)* has collapsed to a slightly broadened singlet at 1.56 ppm (1 H).

Thermolysis and hydrolysis independently support structure *(4)*. *(4a)* remains unchanged at 130 °C. After 27 h at 150 °C quantitative decomposition into *tert*-butylethylene[9] and 2,4-dimethyl-3-pentyl isocyanide[9] has occurred. Not



	R^1	R^2
a	2,4-dimethyl-3-pentyl-	H
b	2,4-dimethyl-3-pentyl-	D
c	methyl-	H
d	isopropyl	H
e	*tert*-butyl	H

even traces (<0.5%) of methyleneaziridines [*e.g. (5a)*], the expected products of a valence isomerization, could be detected. *Thus, there is either no favorable path to the heterocyclic isomers available or the latter are less stable than (4a) by more than 3 kcal/mol.* Experiments to settle this question are under way.

The recently described[3], but unconfirmed[10], isolation of *(6e)* in the reaction of 1,3-di-*tert*-butylaziridinone with methylmagnesium iodide followed by work-up using aqueous ammonium chloride prompted the postulation

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of the steps *(5e)→(4e)→(6e)*. However *(4a)*, which differs only slightly from *(4e)*, could be recovered in 66% yield after 24-h treatment with aqueous ammonium chloride. Hydrolysis of *(4a)* and *(4b)* requires drastic conditions (KOH in dioxane/water, 24 h, 100 °C) and affords 70% of *(7a)*[9] and *(7b)*, respectively. The independently prepared *(6a)* could not be detected by tlc. This regiospecificity of ring opening (path B) parallels the course of the Favorskii rearrangement[5,6]. The described variation of this reaction opens novel synthetic possibilities.

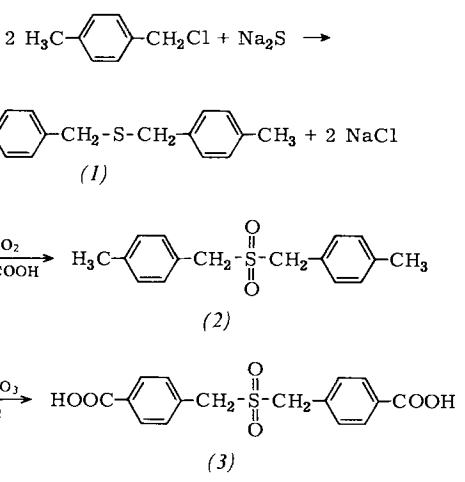
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4,4'-Sulfonyldimethylenedibenzoic Acid

By *Helmut Müller*[*]

Bis(4-methylbenzyl) sulfide *(1)* is known[1] to be accessible by reaction of 4-methyl-1-bromomethylbenzene with an alcoholic solution of K_2S. We have also prepared *(1)* by treatment of 4-methyl-1-chloromethylbenzene with Na_2S. Oxidation of *(1)* by, *e.g.*, HNO_3 under the conditions required for oxidation of methyl to carboxyl groups gave terephthalic acid as major product.

However, if *(1)* is initially oxidized to bis(4-methylbenzyl) sulfone *(2)*, continued oxidation by air in acetic acid or by HNO_3 gives 4,4'-sulfonyldimethylenedibenzoic acid [bis(4-carboxybenzyl) sulfone] *(3)*. Compound *(3)* is also



formed on reaction of 4-chloromethylbenzonitrile or methyl 4-chloromethylbenzoate with Na_2S followed by oxidation of the resulting sulfide to the sulfone, which is then hydrolyzed.

The resistance of the methylene groups to oxidation should ensure that *(3)* has an interesting future as a starting material for the production or modification of polyesters and polyamides.

Procedure:

4-Methyl-1-chloromethylbenzene (70 g) is added dropwise to a refluxing mixture of $Na_2S \cdot 9H_2O$ (90 g), water (75 ml), and methanol (20 ml); refluxing is then continued for 5 h. Compound *(1)* (55.5 g, 92%) crystallizes on cooling. Compound *(1)* (25 g), glacial acetic acid (150 ml), and 30% H_2O_2 (50 ml) are refluxed together for 30 min. Addition of water (100 ml) to the reaction mixture furnishes compound *(2)* (22.4 g, 79%).—A mixture of *(2)* (20 g) and 20% HNO_3 (300 g) is heated to 170 °C in an autoclave for 5 h. On cooling compound *(3)* can be filtered off, washed, and dried. We obtained 20.1 g (82%) of *(3)*, neutralization number 328 mg KOH/g (calc. 336). *(3)* was converted into the dimethyl ester and recrystallized, m. p. 228—229 °C.

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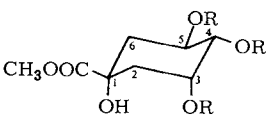
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[1] *L. Martynowicz*, Kosmos *35*, 594 (1910); Chem. Zbl. *1910* II, 1048.

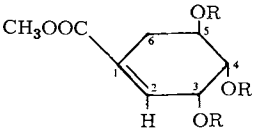
A Stereospecific Conversion of (−)-Methyl Tri-*O*-benzoylquinate to the Corresponding (−)-Methyl Shikimate

By *J. Cleophax*, *D. Mercier*, and *S. D. Géro*[*]

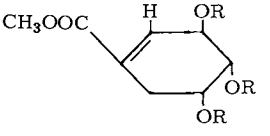
(−)-Shikimic acid, first isolated from the fruits *Illicium religiosum*[1], has been shown to be a biogenetic key link in aromatic biogenesis[2]. For its preparation, numerous total[2-3] and enzymatic[4] syntheses have been reported; the acid has also been obtained[5] from (−)-quinic acid[**]. We report in this communication a simple conversion of the (−)-methyl 3,4,5-tri-*O*-benzoyl-quinate *(2)* into the corresponding shikimate *(4)*. The requisite starting material *(2)* could be obtained[6] by a selective benzoylation of (−)-methyl quinate *(1)*.



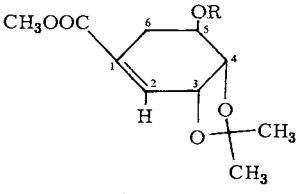
(1), R = H
(2), R = COC_6H_5



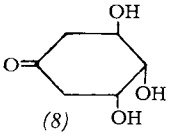
(3), R = H
(4), R = COC_6H_5



(5), R = COC_6H_5



(6), R = H
(7), R = $COCH_3$



(8)

Treatment of the (−)-methyl 3,4,5-tri-*O*-benzoyl-quinate *(2)* with sulfuryl chloride (SO_2Cl_2)/pyridine in anhydrous chloroform at −70 °C for two hours and then at −10 °C for 1 hour, gave a syrupy product in quantitative yield, which was crystallized from methanol, giving (−)-methyl 3,4,5-tri-*O*-benzoyl-shikimate, m. p. 60—62 °C, $[\alpha]_D$ −227° (c = 1.3; $CHCl_3$), 78% yield.

Dehydration of the "tertiary alcohol" *(2)* might give rise to the unsaturated ester *(5)*. The presence of the latter could not be detected by thin-layer chromatography. The NMR spectrum of the ester *(4)* did not provide clear evidence of the location of the double bond, due to the

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[**] IUPAC-IUB Nomenclature Rules for Cyclitols; European J. Biochem. *5*, 1 (1968).

overlapping multiplets from H-2-vinylic and aromatic protons in the vicinity of 7 ppm. In order to prove unequivocally the structure of the dehydration product, the tribenzoate *(4)* was converted by standard procedures into (−)-methyl 5-*O*-acetyl-3,4-*O*-isopropylidene-shikimate *(7)*.

Treatment of (−)-methyl 3,4,5-tri-*O*-benzoyl-shikimate *(4)* with catalytic amounts of anhydrous methanolic-sodium methoxide yielded (−)-methyl shikimate *(3)*, m.p. 112 to 114 °C, $[\alpha]_D$ −130° (c = 1.88; ethanol), [Ref. [7]: m.p. 115 °C, $[\alpha]_D$ −139° (c = 2; ethanol)]. The latter readily condensed with acetone in the presence of anhydrous copper sulfate to yield the syrupy (−)-methyl 3,4-*O*-isopropylidene-shikimate *(6)*. Acetylation of *(6)* using acetic anhydride/pyridine furnished the ester *(7)*, m.p. 72—74 °C, $[\alpha]_D$ −69° (c = 1.15; chloroform), [Ref. [8]: m.p. 75 to 76 °C].

The 100-MHz NMR spectrum of the ester *(7)* in $CDCl_3$, obtained with the aid of spin decoupling, is compatible only with the structure given. The partial spectrum of *(7)* showed: signals at δ = 6.79 (H-2/quintet), 5.10 (H-5/br. m), 4.65 (H-3/br. m), 4.15 ppm (1 H/t). Irradiation of the vinylic proton H-2 caused the broad multiplet centered at 4.65 ppm to collapse to a form of doublet, $J_{3,4}$ = 6 Hz. The fact that the one-proton multiplet H-5 at 5.10 ppm was absolutely unchanged, excludes unequivocally the presence of the isomer *(5)* in the dehydration procedure. Since trihydroxycyclohexanone *(8)* can be readily converted *via* the triacetyl-[9] or 3,4-isopropylidene derivative[10] into labeled (−)-quinic acid, this method provides a simple route to the specifically labeled shikimic acid.

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Preparation of Tris(chloromethyl)amine, $N(CH_2Cl)_3$

By *Ekkehard Fluck* and *Peter Meiser*[*]

Tris(chloromethyl)amine, $N(CH_2Cl)_3$, *(1)*, was first described by *Moeller* and *Westlake*[1] in 1967. They obtained the compound by reaction of aminomethanesulfonic acid, $H_2NCH_2SO_3H$, or the sodium salt of nitrilotrimethanesulfonic acid, $N(CH_2SO_3Na)_3$, with phosphorus pentachloride. In the former case the compound is formed in only very small amounts, in the latter the yield is 23%.

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We have now found that tris(chloromethyl)amine is readily accessible by reaction of phosphorus pentachloride with hexamethylenetetramine, $N_4(CH_2)_6$. The reactants are mixed in a molar ratio of 3:1 and refluxed in benzene or methylene chloride or heated to 100 °C without solvent. Formation of *(1)* according to eq. (1)

$$N_4(CH_2)_6 + 3\,PCl_5 \longrightarrow \underset{(1)}{N(CH_2Cl)_3} + \underset{(2)}{[N(CH_2)PCl_4]_3} \qquad (1)$$

proceeds quantitatively; product *(2)* cannot, however, be isolated. The mechanism of formation of *(1)*, its chemical properties, and the nature of the other products [formed from *(2)*] will be reported later[2]. *(1)* is a colorless, crystalline solid, m.p. 93 °C; NMR (CH_2Cl_2): τ = 4.9; M.W.: 162 (calc.), 156 (cryoscopic, benzene); correct elemental analysis.

Procedure:

A mixture of finely ground hexamethylenetetramine (7.0 g, 0.05 mol), PCl_5 (41.8 g, 0.2 mol), and dry CH_2Cl_2 (150 ml) is refluxed with gentle stirring for 20 h in a 250-ml round-bottom flask fitted with a reflux condenser and drying tube. The solvent is then distilled off; the final solvent residues are removed *in vacuo*, whereupon small amounts of unreacted phosphorus pentachloride may also sublime over. Compound *(1)* is sublimed from the crystalline residue at 70—80 °C/1.5 torr and trapped on a cold-finger; yield 8.0 g (100%). The product can be purified by resublimation or by recrystallization from CH_2Cl_2.

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[2] *E. Fluck* and *P. Meiser*, to be published.

Base-Catalyzed Addition of Oxazol-5-ones to Activated Multiple Bonds[1]

By *Wolfgang Steglich, Peter Gruber, Gerhard Höfle*, and *Wolfgang König*[*]

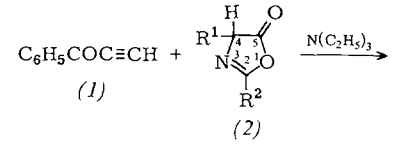
The use of oxazol-5-ones as nucleophilic reactants in Michael additions has hitherto hardly been studied[2, 3]. Since oxazolone anions are ambifunctional[4, 5] they should, in principle, react with activated multiple bonds at C-2, at C-4, and at the exocyclic oxygen. We have found that the site of reaction is determined primarily by the kind of activated multiple bond.

Thus benzoylacetylene *(1)* adds exclusively to position 4 of 4-isopropyl-2-phenyloxazol-5-one *(2a)*. With triethylamine as a catalyst, *(1)* reacts in methylene chloride at as low a temperature as −10 °C within a few minutes to give the *cis*-olefin *(3a)*, which is converted into the *trans* isomer *(4a)* on brief warming to 100 °C.

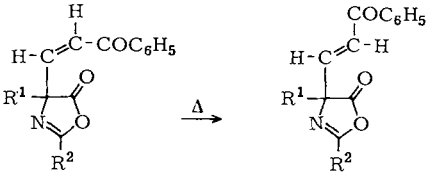
The proclivity of *(1)* to add at position 4 is so pronounced that it is influenced but little by steric and electronic effects in the oxazolone anion. Thus 4-*tert*-butyl-2-phenyloxazol-5-one *(2b)* and 4-isopropyl-2-(*p*-nitrophenyl)oxazol-5-one

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smoothly form the 4-adducts *(3)* which rearrange to *(4b)* and *(4c)* on heating (Table 1). No less than a 2-trifluoromethyl group is required to modify the electron distribution in the anion sufficiently to direct *(1)* to position 2[6].



(1) *(2)*

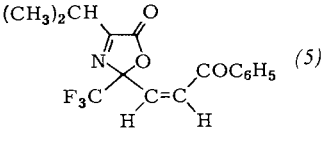


(3) *(4)*

Table 1. 4,4-Disubstituted oxazol-5-ones [a].

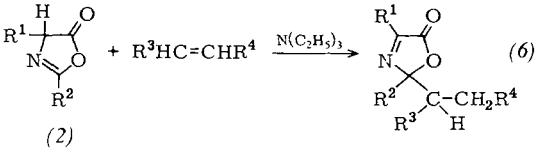
Cpd.	R^1	R^2	Yield (%)	M.p.(°C)
(3a)	$CH(CH_3)_2$	C_6H_5	96	65.5
(4a)	$CH(CH_3)_2$	C_6H_5	75	89.5
(4b)	$C(CH_3)_3$	C_6H_5	70	80
(4c)	$CH(CH_3)_2$	p-$NO_2C_6H_4$	73	114

[a] All compounds gave correct elemental analyses.



(5)

Reaction of 2-trifluoromethyl-4-isopropyl-2*H*-oxazol-5-one with *(1)* proceeds quantitatively, once again *via trans* addition, to give the pseudooxazolone *(5)*.



(2) *(6)*

Table 2. 2,2-Disubstituted pseudooxazol-5-ones [a].

Cpd.	R^1	R^2	R^3	R^4	Yield (%)	M.p.(°C)
(6d)	$CH(CH_3)_2$	C_6H_5	H	CN	98	oil [b]
(6e)	$CH(CH_3)_2$	n-C_5H_{11}	H	CN	95	oil [b]
(6f)	$CH(CH_3)_2$	C_6H_5	CO_2CH_3	CO_2CH_3	92	71
(6g)	$CH(CH_3)_2$	C_6H_5	CN	CN	86	121

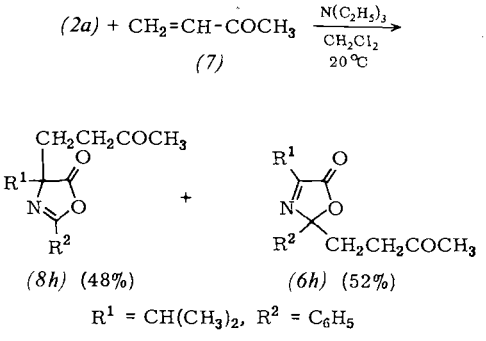
[a] All compounds gave correct elemental analyses.
[b] Loses CO_2 on distillation [8].

The group of reagents that add exclusively to position 2 of 2,4-disubstituted oxazolone anions includes acrylonitrile, fumaric and maleic esters, and the corresponding dinitriles. Reaction furnished 2,2-disubstituted pseudooxazolones *(6)* (Table 2). They can be used for 3C-homologization of carboxylic acids[7].

Dimethyl acetylenedicarboxylate, acrolein, and methyl vinyl ketone *(7)* add to both position 2 and position 4, giving mixtures of *(6)* and 4,4-disubstituted oxazolones *(8)*[9]. The reaction of *(2a)* with *(7)* is shown as an example.

Under analogous conditions dimethyl acetylenedicarboxylate and acrolein afford the 2-adducts *(6)* in 34 and 64% yield, respectively. The product ratio *(6h)*/*(8h)* can be varied within limits by modification of the reaction conditions. If triethylamine is replaced by ethyldiisopropylamine, for example, the proportion of *(6h)* falls to 30%; on refluxing with triethylamine in carbon tetrachloride it rises to 70%.

All the 4-isopropyl-2-phenyl derivatives *(6)* and *(8)* studied can readily be distinguished on the basis of their



(8h) (48%) *(6h)* (52%)

$R^1 = CH(CH_3)_2$, $R^2 = C_6H_5$

NMR spectra (in $CDCl_3$). In *(8)* the methyl protons give two adjacent doublets ($\delta \approx 0.93$ and 1.05 ppm, $J = 7$ Hz) which overlap extensively (1.28 and 1.32 ppm) in the case of *(6)*. The methine signal of *(6)* appears considerably farther downfield (3.0 ppm) than that of *(8)* (2.1 ppm). Finally, the phenyl protons of *(6)* give a broad signal at $\delta \approx 7.5$ ppm which is resolved into two separate multiplets at 7.5 and 8.0 ppm (3 and 2 protons, respectively) in *(8)*.

General procedure:

Triethylamine (3—10 mmol) diluted with methylene chloride is added dropwise to a stirred solution of oxazol-5-one (10 mmol) and an activated alkene (alkyne) (10 mmol) in methylene chloride (30 ml). With highly reactive electrophiles (*e.g.* benzoylacetylene or fumaronitrile) only 3 mmol of triethylamine are used, with less reactive ones (*e.g.* fumaric ester) up to 10 mmol. In the former case the reaction time is just a few minutes, in the latter the reaction mixture is allowed to stand for 2—6 h at room temperature. The triethylamine is extracted with ice-cold 0.1 N HCl and the organic phase is dried and evaporated down *in vacuo*. The adducts are obtained very pure and if required can be recrystallized from chloroform/light petroleum.

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[2] *A. Dzugay, I. Z. Siemion*, and *Z. Ojrzynski*, Roczniki Chem. *40*, 1329 (1966).

[3] *T. Hiraoka* and *Y. Kishida*, Chem. Pharm. Bull. (Tokyo) *16*, 1576 (1968).

[4] *W. Steglich* and *G. Höfle*, Chem. Ber. *102*, 883 (1969).

[5] *W. Steglich* and *G. Höfle*, Chem. Ber. *102*, 1129 (1969).

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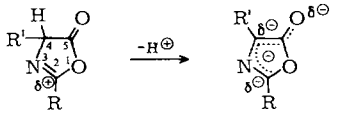
[8] *P. Gruber*, Dissertation, in preparation.

[9] Exclusive addition to position 2 occurs with 2-trifluoromethyl-2*H*-oxazol-5-ones.

Chain Lengthening of Carboxylic Acids by Three Carbon Atoms *via* Oxazol-5-one Anions[1]

By *Wolfgang Steglich* and *Peter Gruber*[*]

The carbon atom in position 2 of oxazol-5-ones, the electrophilic center of a masked carboxyl group, becomes nucleophilic on transition to the oxazolone anion[2].



This effect permits extension of the chain of carboxylic acids by three carbon atoms.

The starting point is the corresponding *N*-acyl-DL-valine *(1)* which is accessible in good yields by Schotten-Baumann reaction[3]. Brief warming with 3—5 mol. equiv. of acetic anhydride to 80—100 °C affords the oxazol-5-one *(2)*, which is treated with acrylonitrile/triethylamine in methylene chloride without prior isolation to give the pseudo-oxazolone *(3)*[1,4]. Hydrolysis with dilute alkalis or acids affords γ-keto nitriles *(4)* or γ-keto acids *(5)*, depending upon the reaction conditions, which are readily separable from accompanying α-ketoisovaleric acid.

Since all steps proceed in good yields and are simple in execution [*(1)* → *(4)* requires no isolation of intermediates] (Table 1), the technique represents a real alternative to hitherto established methods of 3C homologization of carboxylic acids[5-7].

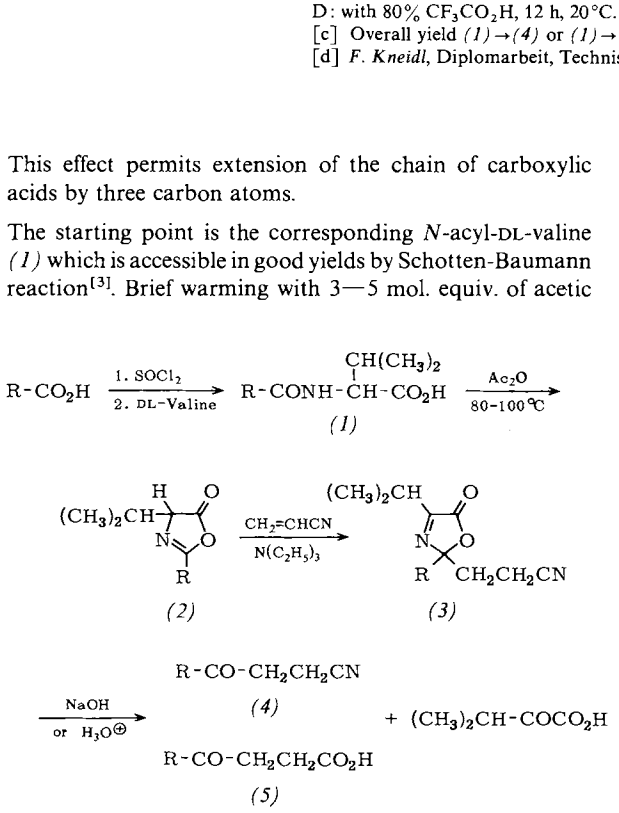


Table 1. Compounds of types *(4)* and *(5)* prepared; reaction conditions.

R [a]	*(1)* yield (%)	*(1)* → *(2)* time/temp. (min/°C)	*(2)* → *(3)* time (h)	*(3)* → *(4)* time (h)/ method [b]	*(4)* yield (%) [c]	*(4)* m.p. (°C)
C_6H_5	90	5/80	3	2/A	89	76
				2/C	82	
m-Cl-C_6H_4	88	10/95	3	2/A	84	52
p-NO_2-C_6H_4	87	5/80	2.5	2/A	88	117.5
				2/D	80	
2-Brom-3,4,5-trimethoxy-phenyl [d]	88	10/100	4	3/A	74	92
1-Naphthyl	91	7/80	4	3.5/A	83	63
$^1/_2$ *p*-Phenylene	80	5/125	4	4/A	74	174
				3/C	63	
2-Furyl	83	15/100	6	2/A	55	76
				(3) → *(5)*		*(5)*
$C_6H_5CH_2$	82	10/100	3	10/B	70	56
n-C_5H_{11}	82	10/80	7	10/B	86	66

[a] All compounds hitherto not described in the literature gave correct elemental analyses.
[b] A: hydrolysis with 1N NaOH; B: with 3N NaOH; C: with 25% H_2SO_4/dioxane (2.5—1:1), 1—3 h, 60 °C; D: with 80% CF_3CO_2H, 12 h, 20 °C.
[c] Overall yield *(1)* → *(4)* or *(1)* → *(5)*.
[d] *F. Kneidl*, Diplomarbeit, Technische Universität München 1971.

General procedure:

Compound *(1)* (0.1 mol) is cyclized with acetic anhydride (0.3—0.5 mol) under the conditions given in Table 1. The reaction mixture is concentrated under vacuum in a rotary evaporator and vacuum-distilled twice with toluene. The residue is dissolved immediately in methylene chloride (40 ml) and treated with acrylonitrile (0.2 mol) at −20 °C. Triethylamine (0.05 mol) in methylene chloride (10 ml) is added dropwise within 30—60 min to the ice-cooled reaction mixture, which is stirred for the prescribed time and then evaporated under vacuum in a rotary evaporator.

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[1] Reactions of oxazol-5-one anions, Part 7.-Part 6: *W. Steglich, P. Gruber, G. Höfle*, and *W. König*, Angew. Chem. *83*, 725 (1971); Angew. Chem. internat. Edit. *10*, 653 (1971).

[2] For compounds having nucleophilic acyl groups see article by *D. Seebach*, Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969).

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[4] NMR check is advisable: Multiplet due to α-CH proton (δ ≈ 4.9 ppm, in $CDCl_3$) of *(1)* is transformed to doublet (δ ≈ 4.4 ppm, $J = 5$ Hz) on cyclization to *(2)* which can be split further by homoallylic coupling. It disappears on completion of acrylonitrile addition.

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Residual triethylamine is removed by dissolution in ethyl acetate and extraction with cold 0.1 N HCl. The organic phase is evaporated down, 1 N NaOH (300 ml) is added followed by enough methanol, THF, or dioxane to give a homogeneous solution. The mixture is stirred for the prescribed length of time, evaporated down to half its original volume *in vacuo*, and extracted three times with ethyl acetate [after prior acidification in the case of *(5)*!]. If necessary the extract is decolorized with animal charcoal, dried over $MgSO_4$, and the solvent is evaporated off. The resulting oils soon crystallize on standing.

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Sequence of Highest Occupied Molecular Orbitals in the Phosphorin System[1, 2]

By *Helmut Oehling*, *Werner Schäfer*, and *Armin Schweig*[*]

The aromatic phosphorins, which are analogs of pyridine, contain a trivalent phosphorus atom of coordination number 2 whose bonding has hitherto hardly been studied. A quantum-mechanical study[3] has shown that the highest occupied molecular orbital (HOMO) is a π-MO, whereas the corresponding orbital in pyridine describes the lone pair (n-MO) on the nitrogen atom. The fundamental importance of the HOMO for properties and reactivity of a compound prompted us to seek experimental confirmation of the theoretical predictions by studying the photoelectron spectrum of 2,4,6-tri-*tert*-butylphosphorin *(1)*.

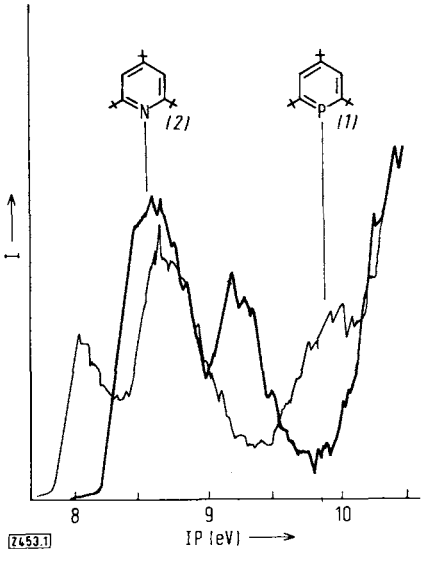


Fig. 1. Sections of photoelectron spectra of 2,4,6-tri-*tert*-butylpyridine *(2)* and 2,4,6-tri-*tert*-butylphosphorin *(1)* in arbitrary intensity units. *IP* = ionization potential.

Figure 1 shows a section of the photoelectron spectrum of *(1)* and, for comparison, of 2,4,6-tri-*tert*-butylpyridine *(2)*[4, 5].

The band maxima in the spectrum of *(1)* lie at 8.0, 8.6, and 10.0 eV, those in the spectrum of *(2)* at 8.6 and 9.3 eV. As expected, the phosphorins are more readily ionized than corresponding pyridines. The band maxima in unsubstituted pyridine are found at 9.6, 9.7, and 10.5 eV[6]. Hence the three *tert*-butyl groups in *(2)* lower the ionization potential (*IP*) by 1.0 to 1.2 eV.

The size of molecules *(1)* and *(2)* precludes direct CNDO/2 calculations[7]; instead calculations were performed on 2,4,6-trimethylphosphorin *(3)* and 2,4,6-trimethylpyridine *(4)*. A series of model calculations on the mono-, di-, and tri-methyl and the mono- and di-*tert*-butyl substituted compounds showed that replacement of a methyl by a *tert*-butyl group shifts the orbital energy by an additive component but that the orbital sequence is retained. For compound *(4)* it is n, π, π, σ and for *(3)* π, n, σ, π (see Fig. 2). These results strongly suggest that the first photoelectron band of *(2)* arises from overlap of an n- and a π ionization, and the second band from a π ionization. The intensity ratio of the first to the second band (2:1) may be regarded as supporting evidence. The same orbital sequence has recently also been suggested for pyridine itself by photoelectron spectroscopy[8].

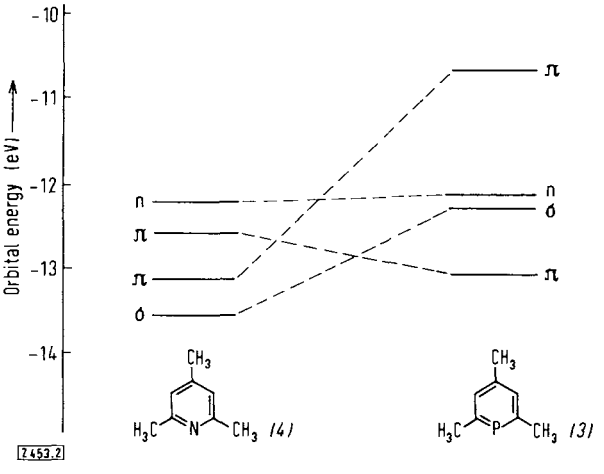


Fig. 2. Correlation diagram for model compounds *(3)* and *(4)*.

According to Figure 2 the first and third band of phosphorin *(1)* should be assigned to a π ionization, while the second band should result from an n- and a σ ionization. Experience shows, however, that semiempirical valence-electron calculations on unsaturated systems afford σ orbitals of too high energy[9], thus making assignment of π, n, π, and σ ionization to the three photoelectron bands more likely.

It is to be expected from Figure 2 that the *IP* of the lone pairs of *(1)* and *(2)* are almost equal. The *IP* of the lone pairs of NH_3 and PH_3 also differ by only 0.25 eV[10]. On the basis of these findings it would appear likely that the n-ionization bands are hidden under the low *IP* side of the bands at 8.6 eV in *(1)* and *(2)*.

The changes in MO energies (Fig. 2) on going from the pyridine to the phosphorin series can be readily interpreted in terms of hybridization and conjugation effects on the basis of the contributions of the atomic orbitals (AOs) on the hetero atom and the neighboring C atoms. Thus the main contributions to the n-MO are made by the 3s- and $3p_x$-AOs of the phosphorus atom and the 2s- and $2p_x$-AOs of the nitrogen, the former having the higher energy. In the phosphorin this energy difference is compensated by a considerably greater contribution of the s-AOs so that the energies of the n-MOs are only slightly different in the two

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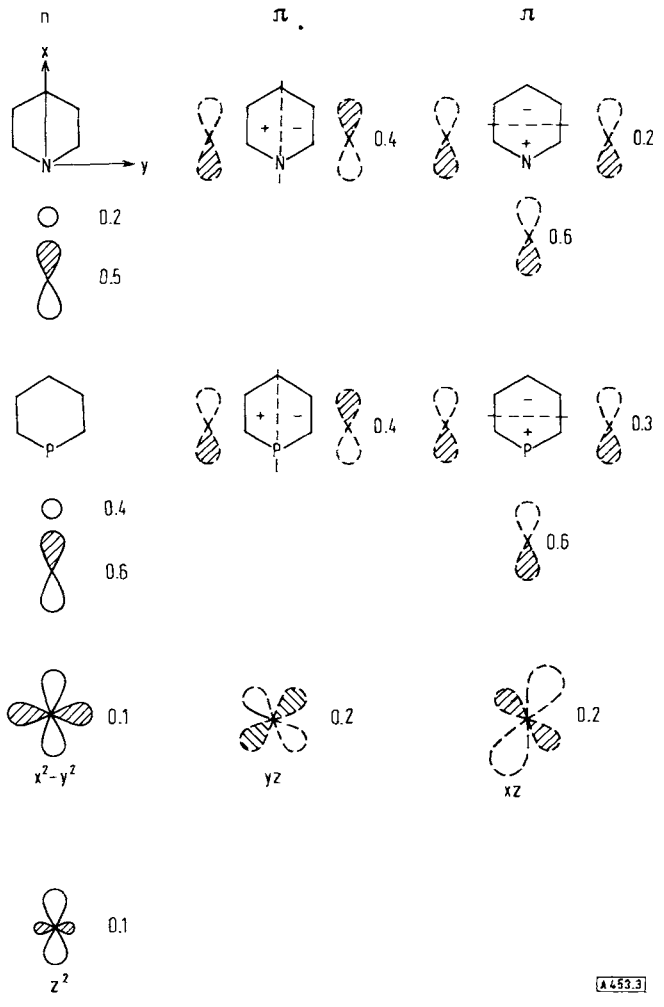


Fig. 3. Contributions of hetero atom AOs to the n-MO and of hetero atom neighboring C atom AOs to the two highest occupied π-MOs. The π-AOs are shown hatched to distinguish them from the σ-AOs.

compounds: The same change in the mixing ratio of s-AO and p-AO was also found on going from NH_3 to PH_3. In pyridine the highest π-MO has a node at the hetero atom whereas in phosphorin the conjugation of the corresponding π-MO can extend over the phosphorus atom *via* the $3d_{yz}$-AO. This d-electron effect leads to a lowering of the energy of this π-MO in phosphorin. The energy of the next lower π-MO in pyridine having an antinode on the hetero atoms is raised so drastically in phosphorin that it is promoted to the HOMO. The reason lies in the markedly less favorable $3_{p\pi}2_{p\pi}$ conjugation between the hetero atom and the neighboring C atoms in phosphorin compared with the corresponding $2_{p\pi}2_{p\pi}$ conjugation in pyridine. Any possible conjugative lowering of the energy of this MO by admixture of the $3d_{xz}$-AO of the P atom is thus overcompensated.

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[1] Paper read at EUCHEM Conference "Organic Chemistry of Phosphorus and the Heavy Elements of Group Va", Schloss Elmau, March 30—April 2, 1971.

[2] We acknowledge support of this work by the Deutsche Forschungsgemeinschaft and thank the Deutsches Rechenzentrum, Darmstadt, for performing the calculations.

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[5] The photoelectron spectra of solids *(1)* and *(2)* were recorded on an instrument produced by Perkin-Elmer Ltd. (Beaconsfield, England). Calibration with O_2, bands at 12.08 and 18.17 eV. We are indebted to Ing. *H. J. Lempka* and Dr. *J. N. A. Ridyard* for recording the spectra. The spectrum of *(1)* was also measured independently by *E. Heilbronner et al.* The first maxima of this spectrum lie at 7.95, 8.55, and 9.95 eV. We are very grateful to Prof. *Heilbronner* for communication of these data and for pointing out a calibration error in the spectra originally recorded in England.

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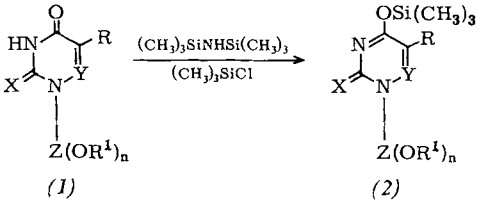
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A Simple New Synthesis of Cytidines[**]

By *Helmut Vorbrüggen* and *Ulrich Niedballa*[*]

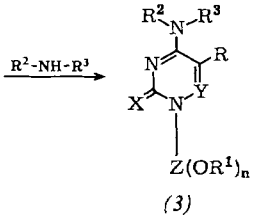
In the presently known methods for the conversion of uridines into cytidines, the alcoholic hydroxyl groups of uridines have to be acylated before the 4-position can be activated by reaction with P_2S_5/pyridine[1] or Vilsmeyer reagent[2] to give the corresponding cytidines on subsequent reaction with NH_3 or amines.

Protection of the alcoholic hydroxyl groups, activation of the 4-position, and reaction with NH_3 or amines can be combined if one silylates uridines *(1)* (X=O, Y=CH, Z=D-ribofuranose, R^1=H) to give the 4-trimethylsiloxy derivatives *(2)* [$R^1 = OSi(CH_3)_3$] and treats *(2)* in analogy to the 4-*O*-alkyluridines[3] *in situ* with NH_3 or amines to form the cytidines *(3)* (R^1=H). Since NH_3 is liberated on silylation with hexamethyldisilazane (HMDS), uridine and thymidine can thus be converted by HMDS and added



(1) R^1 = H, Ac, Bz

(2) R^1 = $Si(CH_3)_3$, Ac, Bz



(3) R^1 = H, Ac, Bz

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[**] Synthesis of Nucleosides, Part 5.—Part 4: *H. Vorbrüggen* and *U. Niedballa*, Tetrahedron Lett. *1970*, 3571.

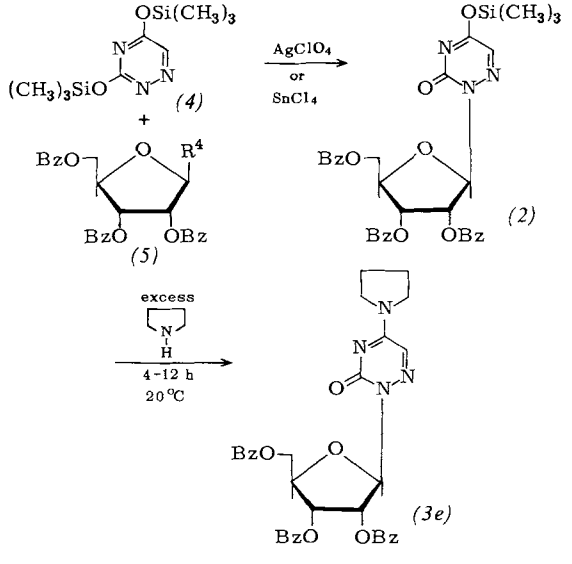
excess NH_3 in one step into the corresponding cytidines by heating in an autoclave. Before reaction of *(2)* with primary amines, the HMDS should be distilled off since primary amines are silylated[4] on heating with HMDS and will no longer react with *(2)*. *O*-Acylated uridines *(1)* (R^1 = Ac, Bz) react similarly to give the *O*-acylated cytidines *(3)* (R^1 = Ac, Bz) *via (2)* (R^1 = Ac, Bz).

persilylated derivatives *(2)* [$R^1 = Si(CH_3)_3$]. For the silylation of acylated uridines, especially of acylated 6-azauridines, several hours' heating in benzene with HMDS and trimethylsilyl chloride is sufficient. The reactions of 4-trimethylsiloxy derivatives *(2)* with amines to the free (R^1 = H) or *O*-acylated (R^1 = Ac, Bz) cytidines *(3)* are compiled in the Table.

	(2)				*(3)*					
	X	Y	R	$Z(OR^1)_n$	amine R^2—NH—R^3	solvent	*T* (°C)	*t* (h)	yield (%)	m.p. (°C)
(a)	O	CH	H	2,3,5-tris(*O*-trimethylsilyl)-D-ribofuranose	NH_3	HMDS	165 25 atm	48	80	230 (dec.)
(b)	O	CH	H		pyrrolidine	— [a]	140	20	74	209—11
(c)	O	N	H		pyrrolidine	HMDS, pyridine	120	20	57	164—65
(d)	O	CH	H		*N,N*-dimethylethylenediamine	— [a]	65	120	62	184—85
(e)	O	N	H	2,3,5-tri-*O*-benzoyl-D-ribofuranose	pyrrolidine	HMDS benzene	22	15	92	186
(f)	O	N	H		benzylamine	HMDS benzene	22	65	63	178—79
(g)	S	N	H	2,3,4,6-tetra-*O*-acetyl-D-glucopyranose	β-phenylethylamine	HMDS benzene	22	72	84	212
(h)	S	N	H		pyrrolidine	HMDS benzene	22	72	83	162
(i)	O	CH	CH_3	3,5-bis(*O*-trimethylsilyl)-2-deoxy-D-ribofuranose	NH_3	HMDS [b]	150 25 atm	96	65	193 (hydrate)
(j)	O	CH	CH_3		β-phenylethylamine	— [a]	120	144	55	182—184

[a] The HMDS was evaporated off in these experiments *before* addition of the amine.
[b] The reaction was carried out in a glass-lined autoclave.

The free uridines *(1)* (R^1 = H) are converted by standard methods[4] on 4—16 hours' heating with HMDS and traces of trimethylsilyl chloride as catalyst into the activated



R^4 = Cl; $AgClO_4$ in C_6H_6 ⟶ 46% *(3e)*
R^4 = OAc; $SnCl_4$ in $ClCH_2CH_2Cl$ ⟶ 57% *(3e)*

Since the acylated 4-trimethylsiloxy derivative *(2)* (R^1 = Ac, Bz) is also formed as an intermediate in the Silyl-Hilbert-Johnson reaction[5] we have treated the 2,4-bis(trimethylsiloxy) derivative *(4)* of 6-azauracil with the benzoylated D-ribofuranose derivative *(5)* in the presence of $AgClO_4$[6] or $SnCl_4$[7] to give the same intermediate *(2)*, which was converted *in situ* by an excess of pyrrolidine into the acylated cytidine *(3e)* in 46% or 57% yield, respectively. One can thus synthesize acylated cytidines in one step starting from uracils.

Cytidine (3a), R^1 = H:

Uridine (4.88 g, 20 mmol) in HMDS (50 ml) + NH_4Cl (5 mg) was saturated for 30 min at 24 °C with dry NH_3 gas in a 100 ml autoclave and then allowed to react for 48 h at 165 °C/25 atm. After cooling, release of pressure, and evaporation the residue was refluxed for 6 h in methanol, again evaporated, and the residue purified by dissolution in H_2O (100 ml) and treatment with charcoal. After evaporation, 3.9 g = 80% cytidine was obtained, which crystallized spontaneously from ethanol/H_2O, m.p. = 230 °C (dec.).

N^4,N^4-Butylenecytidine (3b), R^1 = H:

Uridine (4.88 g, 20 mmol) in HMDS (100 ml) and trimethylsilyl chloride (0.1 ml) was refluxed with stirring for

16 h at 150 °C in an oil bath. After evaporation of the HMDS, pyrrolidine (4.15 ml, 50 mmol) was added and the mixture heated for 20 h at 140 °C in an oil bath. The excess of pyrrolidine was removed by codistillation with benzene, the residue refluxed for 1 h in methanol (150 ml), the solution decolorized by charcoal, and evaporated. The residue gave 4.4 g = 74% *(3b)*, m. p. = 209—211 °C, on crystallization from ethanol.

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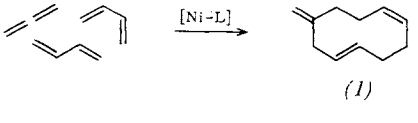
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Catalytic Mixed Oligomerization of Butadiene and Allenes

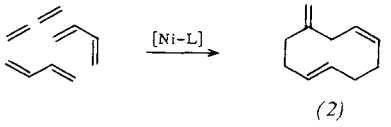
By *Paul Heimbach, Harald Selbeck*, and *Eduard Troxler*[*]

In the presence of nickel(0)-ligand catalysts, butadiene and ethylene or alkynes give *cis,trans*-cyclodeca-1,5-diene[1] or *cis,cis,trans*-cyclodeca-1,4,7-trienes[2, 3].

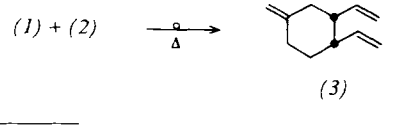
Reaction of allene and butadiene in the molar ratio 1:10 in the presence of a nickel(0)-tris(2-biphenylyl)phosphite catalyst (Ni—L) in an autoclave gives a 35% yield of 8- and 9-methylene-*cis,trans*-cyclodeca-1,5-diene, *(1)* and *(2)* respectively, alongside large amounts of higher oligomers whose structures were not determined. However, if the butadiene-allene mixture is passed into the catalyst solution in such a manner that the steady-state concentration of the allene remains low, then the same catalyst gives a mixture of *(1)* and *(2)* in 69% yield based on reacted allene.



(1)



(2)

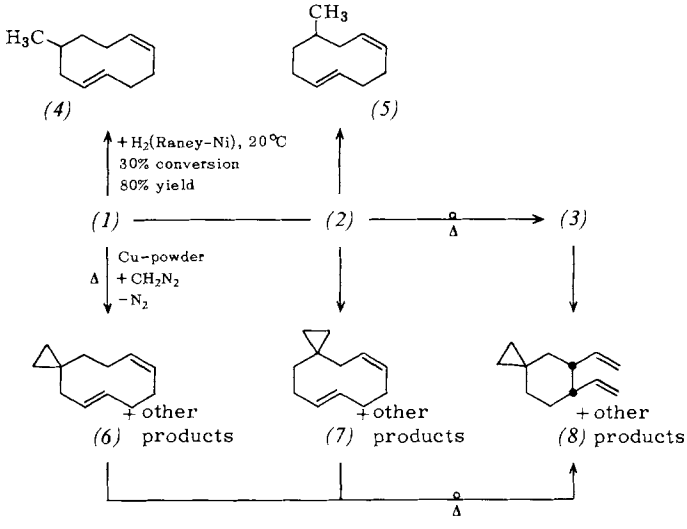


(3)

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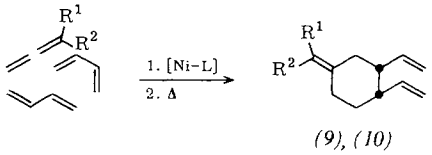
The mixture of *(1)* (63%) and *(2)* (35%) (m. p. 53 °C/1.5 torr, $n_D^{20} = 1.5079$) could be concentrated to 98% by distillation using a spinning-band column. Hydrogenation of *(1)* and *(2)* gives methylcyclodecane. *(1)* can be obtained pure by low temperature recrystallization from ethanol (m. p. 3.5—4.0 °C, $n_D^{20} = 1.5088$). 4-Methylene-*cis*-1,2-divinylcyclohexane *(3)* is formed by Cope-rearrangement on heating of *(1)* and *(2)* to 150 °C. Pure *(3)* boils at 179 °C/760 torr ($n_D^{20} = 1.4848$). ^{1}H-NMR, IR, and mass spectra of the mixture of *(1)* and *(2)* and of the pure compounds *(1)* and *(3)* are in agreement with the structures given.

In the course of this investigation we were also able to assign structures to the isomeric ten-membered rings *(4)* and *(5)* formed catalytically from butadiene and propylene[4], as well as *(6)* and *(7)* from butadiene and methylene-



cyclopropane[4, 5]. Heating of a 1 to 2% solution of diazomethane in *(1)*, a mixture of *(1)* and *(2)*, or in *(3)* with copper powder[8] affords three, six, or three isomeric hydrocarbons in an overall yield of 2 to 3%. *(6)*, *(7)*, and *(8)* present in the mixtures could be assigned unequivocally[6, 7].

Besides *(1)* and *(2)*, catalytic mixed oligomerization of butadiene and allene also gives bis(methylene)-twelve membered rings, consisting of two molecules of butadiene and two of allene, in 5 to 13% yield, independent of the catalyst used. The relative positions of the methylene groups were established, *inter alia*, by hydrogenation (PtO_2/glacial acetic acid) to *cis*- and *trans*-1,3-, 1,4-, and,



(9), (10)

(9), $R^1 = R^2 = CH_3$; b. p. 95 °C/10 torr, n_D^{20} 1.4946 (97%)
(10), R^1 or $R^2 = OCH_3$, R^2 or $R^1 = H$; b. p. 96 °C/8 torr, $n_D^{20} = 1.4953$ (99%)

in low yields, to 1,2-dimethylcyclododecanes which were compared with authentic samples[6, 7].

Reaction of 1,1-dimethylallene[9] or methoxyallene[10] and butadiene in presence of nickel-ligand catalysts gives the *cis,trans*-cyclodeca-1,5-diene derivatives corresponding to *(1)* and *(2)* which were isolated after Cope rearrangement

as the six-membered rings *(9)* and *(10)* in 40% [ligand = tris(2-biphenylyl)phosphite] and 45% yield [ligand = triphenylphosphane] based on reacted 1,2-diene.

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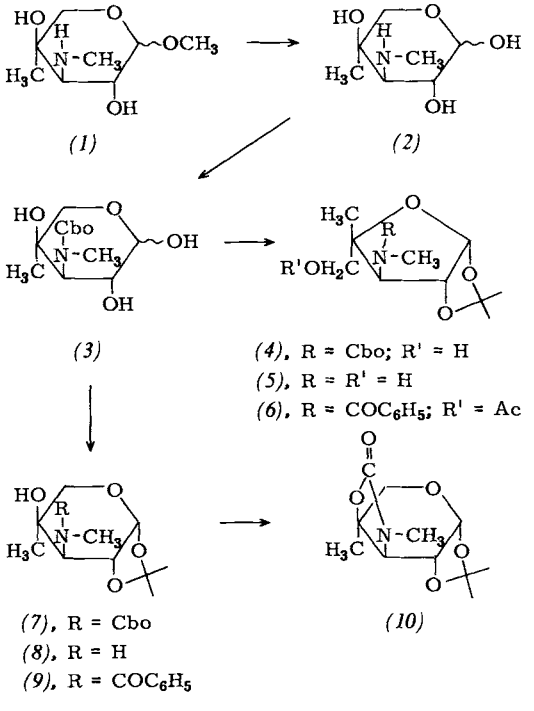
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Configuration of Garosamine, a Branched Chain Amino Sugar[**]

By *Wolfgang Meyer zu Reckendorf* and *Eberhard Bischof*[*]

Garosamine[2] which is obtained by hydrolysis of the gentamycin C_1, C_{1a}, and C_2 complex[1] occupies a special place among the many monosaccharides from antibiotics: It is the only natural branched-chain amino sugar to have been discovered so far. The structure of the methyl glycoside *(1)* of garosamine was confirmed by comparison with synthetic material[3]; however, the configuration of C-4, which is not susceptible to NMR spectroscopy, could only be suggested by IR measurements[3] of the hydrogen bond that may exist between OH at C-4 and NH. These spectroscopic results were later confirmed independently[4]. The cyclization described in the present communication affords chemical proof of the configuration of C-4.



Hydrolysis of the anomers *(1)* (24 h boiling in 1 N HCl) gave the free sugar *(2)* which was converted directly into the benzyloxycarbonyl derivative *(3)* without isolation by treatment with benzyloxycarbonyl chloride in sodium carbonate solution [syrupy liquid; yield 65%; $[\alpha]_D^{20} = +83°$ ($c = 0.9$; methanol)]. On reaction with hydrogen chloride in 2,2-dimethoxypropane (24 h, room temperature) and subsequent separation by layer chromatography (silica gel P; cyclohexane/ethyl acetate 1:1), compound *(3)* gave the pyranose derivative *(7)* [upper zone; syrupy liquid; yield 33%; $[\alpha]_D^{20} = +48°$ ($c = 0.7$; $CHCl_3$)] and the furanose *(4)* [lower zone; syrupy liquid; yield 16%; $[\alpha]_D^{20} = +28°$ ($c = 0.7$; $CHCl_3$)]. The constitutions of the pyranose and furanose forms were established by acylation.

Catalytic hydrogenation of *(7)* proceeded quantitatively to give the base *(8)* [characterized as the hydrochloride; m.p. 201—205 °C; $[\alpha]_D^{20} = +46°$ ($c = 0.5$; methanol)]. On *N*-benzoylation the latter furnished *(9)* [syrupy liquid; yield 43%; $[\alpha]_D^{20} = +38.5°$ ($c = 1$; $CHCl_3$)] which could not be acetylated (tertiary OH). In contrast, hydrogenation of *(4)* gave *(5)* [crystalline hydrochloride; yield 79%; m.p. 210—211 °C; $[\alpha]_D^{20} = +7°$ ($c = 1$; methanol)] which afforded the acetate *(6)* [syrupy liquid; yield 55%; $[\alpha]_D^{20} = -10.5°$ ($c = 1$; $CHCl_3$)] on subsequent *N*-benzoylation (benzoic anhydride/methanol) and acetylation (acetic anhydride/pyridine). Moreover, the mass spectrum of *(5)* (hydrochloride) contains a fragment formed by loss of CH_2OH which is characteristic of furanoses.

The pyranose derivative *(7)* proved very sensitive to alkali. On treatment with an anion exchange resin (Amberlite IRA 400 OH^-) in methanol (2 h, room temperature), *(7)* cyclizes to the oxazolidone *(10)* with elimination of benzyl alcohol [yield 75%; m.p. 123—124 °C; $[\alpha]_D^{20} = \pm 0°$; $[\alpha]_{250}^{20} = -110°$ ($c = 1$; $CHCl_3$); IR: no OH or NH; CO at 1740 cm^{-1}; M.W. 243 (mass spectrum); NMR ($CDCl_3$; δ in ppm): 5.54 (H-1/d); 4.42 (H-2/q); $J_{1,2} = 5$ Hz; 3.79 (H-3); $J_{2,3} = 2.5$ Hz; 3.75 (2 H-5); 1.39, 1.42, 1.59 (3 C—CH_3); 2.97 (N—CH_3)].

A study of models shows that formation of the oxazolidine ring constitutes a proof of the L configuration of C-4. Garosamine is therefore proved as being 3-deoxy-3-methylamino-4-*C*-methyl-L-*arabino*-pentose, in agreement with spectroscopic results.

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[**] We are grateful to the Deutsche Forschungsgemeinschaft for their support of this work and to E. Merck AG for a gift of gentamycin (Refobacin®).

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Problems in the Determination of Very Small Amounts of Elements

By *Günther Tölg*[*]

Selected examples were used to show how analytical procedures for determination of elements in ng and pg quantities can be optimized: this involves special techniques for the decomposition of samples and for separations, with lower blanks and lower losses by adsorption or volatilization, as well as new methods of determination.

Organic matrices can be decomposed in an oxygen plasma excited by microwaves (2450 MHz)[1]; volatile elements (I, As, Se, Cd, *etc.*) are retained in a cold finger attached to the apparatus; Hg in amounts <1 ng are $>90\%$ condensed in a receiver cooled in liquid nitrogen. In cell and tissue samples (*ca.* 1 g), for example, amounts of Be of $<10^{-7}\%$ can then be determined (gas-chromatographically as Be trifluoropentanedionate)[2].

ng amounts of nitrogen can be obtained from many matrices by a modified Kjeldahl method: the ammonia is determined directly in the receiver of a recycling distillation apparatus by coulometry with biamperometric determination of the endpoint[3].

Many cations can be separated in amounts <1 ng by thin-layer chromatography, *e.g.*, as dithizonates, on a *ca.* 2μ-thick film of aluminum oxide produced by anodic oxidation[4]. The aluminum oxide thin film is also useful for separation of organic substances (*e.g.*, metabolites of insecticides, dyes, *etc.*) in amounts of 10^{-9} to 10^{-10} g.

For indirect gas-chromatographic determination of Ni, Zn, and other metals in amounts of 10^{-8} to 10^{-10} g their chelate complexes with polychlorinated xanthates are formed, then separated by thin-layer chromatography, and extracted from the adsorbent by hexane[5]. The xanthates are then decomposed thermally on the column, and the polychlorinated alcohols thus obtained are determined by an electron-capture detector.

1 ng amounts of Se can be similarly obtained by direct gas chromatography[6]: with polychlorinated diols [*e.g.*, 1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene-2,3-bismethanol (Endodiol)] SeO_2 forms volatile selenous esters (Selenodan) which can be detected in amounts as low as 10^{-12} g by an electron-capture detector.

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SELECTED ABSTRACTS

Methods for the measurement of photoluminescence quantum yields are reviewed critically by *J. N. Demas* and *G. A. Crosby*. The pertinent literature is covered through early 1969; luminescence quantum yields of solids are excluded. A chapter discussing absolute methods is followed by an account of published standard quantum yields. Instructions are given for the calibration of light sources, monochromators, and detectors. Corrections necessary for the results of most methods are stated. Finally, recommendations about data presentation are made. [The Measurement of Photoluminescence Quantum Yields. A Review. J. Phys. Chem. *75*, 991—1024 (1971); 147 references, 3 figures]

[Rd 385 IE–H]

Methods of sequence analysis of ribonucleic acids are considered in a review article by *M. A. Billeter*. Such a sequence analysis depends upon the possibility of enzymatic cleavage of the nucleotide chain at defined linkages by specific ribonucleases (T_1-ribonuclease, pancreas ribonuclease) and separation of the resulting oligonucleotides by DEAE chromatography with decreasing pH and by *Sanger*'s fingerprinting technique. The isolated oligonucleotides are subjected to alkaline or enzymatic degradation. A new method of sequence analysis for large ribonucleic acid molecules is illustrated for bacteriophage Qβ-RNA. [Über die Sequenzanalyse an Ribonucleinsäure. Chimia *25*, 181—187 (1971); 22 references, 13 diagrams]

[Rd 391 IE–M]

Grundpraktikum der organischen Chemie (für Chemiker, Physiker, Biologen und Mediziner im ersten Studienabschnitt) (Fundamentals of Practical Organic Chemistry (for Chemists, Physicists, Biologists, and Doctors in their first semesters)). By *E. Poulsen Nautrup*. Vieweg und Sohn, Braunschweig 1969. iv, 72 pp., 13 figs., DM 7.80.

Under the title "Standardmethoden der praktischen Chemie (Standard Methods in Practical Chemistry)", Vieweg und Sohn publish a loose-leaf collection of preparative methods; as a text on the fundamentals of practical organic chemistry, some of these methods have now simply been put together in book form. Thus, the individual methods remain isolated; no attempt has been made to link them up or arrange them in any sort of order that might justify the name "Fundamentals". The criteria for selection remain unclear: for instance, 13 of a total of 72 pages are devoted to preparation and reactions of diazonium salts, at the expense of other preparations and reactions of greater educational value. The instructional value of specific dye syntheses (p. 55) in the training of physicists, biologists, or doctors is dubious. The description of each individual preparation is divided into the following sections: description of the reaction, course of the reaction, general range of application, safety precautions, and general operating instructions.

In the context of a practical manual for beginners, the notes on safety precautions and the general operating instructions, with their detailed information on the amount of time, equipment, and chemicals required, are very useful. However, students would do better not to read the general descriptions of the reactions. There are at present a whole series of organic chemistry textbooks in which established reaction mechanisms are clearly displayed. One wonders, therefore, how anyone could arrive at the reaction mechanisms as formulated here, which are faulty in so many instances that it is just not worth going into details.

Clear and uniform manner of writing is particularly important in a book intended for beginners. When a group is split off from a molecule, the fate of the bonding electron pair should be perfectly clear (see p. 25). Expressions such as "carban-ion" (pp. 18, 29), "positive effect of the benzene nucleus" (p. 18), or "electron-repelling effect of the OH group" (p. 57) just may not occur. Students should therefore be dissuaded from buying this book, despite the fact that it is precisely the beginner who would benefit from the detailed descriptions of the experiments.

Franz Effenberger [NB 978 IE]

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The Present Position of Hemoglobin Research[**]

By Gerhard Buse[*]

Dedicated to Professor Gerhard Braunitzer on the ocassion of his 50 th birthday

Up to the present time hemoglobin has enjoyed pride of place among the objects of study in molecular biology. Investigations on this molecule have culminated in the complete description of its atomic structure in various functional states and point the way for future research on other biopolymers. However, more than just a knowledge of the anatomy of this protein is required before we can make quantitative predictions about its function.

1. Introduction

The red blood pigment hemoglobin is one of the most intensively studied of all macromolecules. More than 500 publications on this topic have appeared during the last two years[1]. The concentrated study of this protein has contributed greatly to knowledge in the field of molecular biology. Only a broad survey can be given in this article, and the selection is subjective; we have been concerned with this molecule mainly from the standpoint of protein chemistry.

The name "hemoglobin" in the title should be taken as a family name. It includes the myoglobins and (as has recently been shown) the erythrocruorin of insects, and possibly also the hemoglobin of leguminous plants[2]. This relationship is confirmed by the reversible binding of O_2 on the Fe^{2+} coenzyme, protoporphyrin IX[3], and by agreement in primary and tertiary structures. No genetic relationship with hemoglobin has so far been found for the other heme proteins that occur in nature, particularly the cytochromes. A possible exception is cytochrome b 562 from *E. coli*[4].

Molecular-biological studies on the hemoglobins began with the X-ray analysis of myoglobin at a resolution of 6 Å, and shortly afterwards at a resolution of 2 Å[5]. This was followed by the conformational analysis of hemoglobin by *Perutz et al.*[6], which showed that this molecule is built up from 2×2 myoglobin-like subunits ($\alpha_2\beta_2$). *Braunitzer et al.*[7] published the primary structure of human hemoglobin in 1961, and *Ingram*[8] interpreted sickle cell anemia as arising from a genetic defect of this molecule. Following these investigations, refinements of the X-ray structures of myoglobin and hemoglobin extending down to atomic resolution, as well as four other X-ray analyses, were published, some 35 primary structures were reported and more than 100 hemoglobin anomalies discovered.

Investigations on the function of this molecule are being carried out at present with the aid of a large number of physicochemical methods. These include kinetic studies with rapid mixing techniques, temperature and field jump methods, flash photolysis, IR spectroscopy, measurement of the optical rotatory dispersion (ORD) and of the circular dichroism (CD), polarography, electron spin resonance spectroscopy (ESR), and recently nuclear magnetic resonance spectroscopy (NMR). The important contributions made by these methods cannot be mentioned in detail here, but have recently been reviewed[9]. The object of the investigations is to clarify the function of this protein on the molecular level and to investigate its genetic formation and modification.

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[**] Abbreviations used:

Mb	Myoglobin
Hb	Hemoglobin
α, β, γ, δ, ε	Peptide chains (subunits) of the hemoglobins
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
NA...B...C...HC	Helical and interhelical regions of the hemoglobins and myoglobins
His β,F8(97)	Notation for the position of an amino acid, *i.e.* histidine of the β chain in position 8 of the F helix, position 97 of the sequence
pMB	*p*-Chloromercuribenzoate
2,3-DPG	2,3-Diphosphoglyceric acid

2. The Primary Structure and Its Variability

2.1. Biosynthesis

The biosynthesis of hemoglobin was investigated in the reticulocyte system of rabbits. It was found that 9S-RNA of the polysome fraction of mouse reticulocytes could be used in a cell-free rabbit reticulocyte system for the synthesis of β chains of Hb. This was the first protein biosynthesis to be carried out by mRNA from mammals in a cell-free system[10]. Rabbit globin can be obtained *in vitro* in the *E. coli* system with rabbit reticulocyte RNA; this is an excellent illustration of the universality of the genetic code. *N*-Acetylvalyl-tRNA is essential here, as it initiates the synthesis on Val NA1α,β(1)[11]. Other experiments showed that the biosynthesis beginning at the amino end is delayed if no heme can be incorporated into the three-dimensional structure of the molecule after about 90 steps of the synthesis; this indicates that the N-terminal parts of the protein released by the ribosomes orient themselves in space even before they are finally released from the point of synthesis.

The peptide chain synthesized in this way contains the information for the three-dimensional folding of the molecule and for the binding of heme, and thus determines the properties of the molecule. It is collinear with the sequence of the DNA codons of the corresponding genes. These cannot be studied directly at present, but have been located on a chromosome arm in the case of the dipterous insect genus *Chironomus*[12]. Evidence of collinearity can also be deduced from a number of observations in sequence analyses on hemoglobin[13] and other proteins.

2.2. Primary Structures

Investigations on sperm-whale myoglobins and on human hemoglobin had already shown the basic types of peptide chains that characterize the myoglobins and hemoglobins of vertebrates. The longest chain type occurs in the monomeric myoglobins with 153 amino acids. The sequences known so far are related; they lack cysteine. Position 9 is deleted in human myoglobin, *i.e.* the chain consists of only 152 amino acids[14] (see Table 1). Hemoglobins in birds, amphibians, and teleosts also exhibit the tetrameric construction from α and β chains, which generally consist of 141 and 146 residues respectively. Cysteine occurs here, but no disulfide bridges are formed. The amino end is acetylated in some cases. Data of this kind have been collected since *1967* by *Dayhoff et al.*[19].

In addition to hemoglobin A and myoglobin, there are also a number of other human hemoglobins, such as fetal hemoglobin F, which contains γ chains instead of the two β chains ($\alpha_2\gamma_2$)[16]. The γ chains are no longer synthesized after birth. There is probably also a fetal myoglobin corresponding to the fetal hemoglobin[15]. Moreover, in addition to HbA, the adult also has about 2% of HbA_2 ($\alpha_2\delta_2$)[17], which contains another non-α chain, *i.e.* the δ chain; an embryonal hemoglobin ($\alpha_2\varepsilon_2$)[18] containing the ε chain, the details of which are not yet known, is observed in very early embryonal stages. The ontogeny of these chains is shown in Figure 1.

A deeper insight into the relations between structure and function is provided by the comparative analysis of phylogenetically distant hemoglobins. The hemoglobin of the sea lamprey *(Petromyzon marinus)*, a primitive jawless vertebrate, is monomeric as HbO_2 and polymeric as Hb.

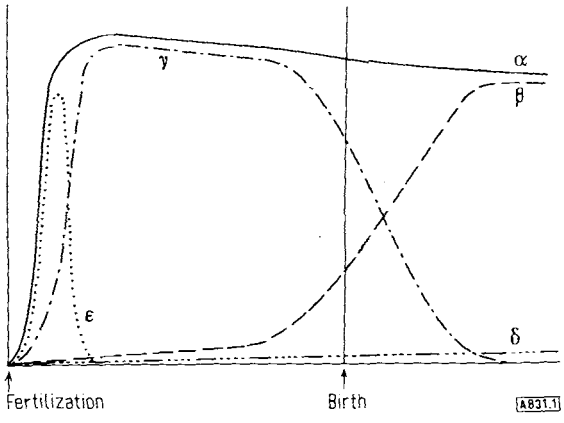


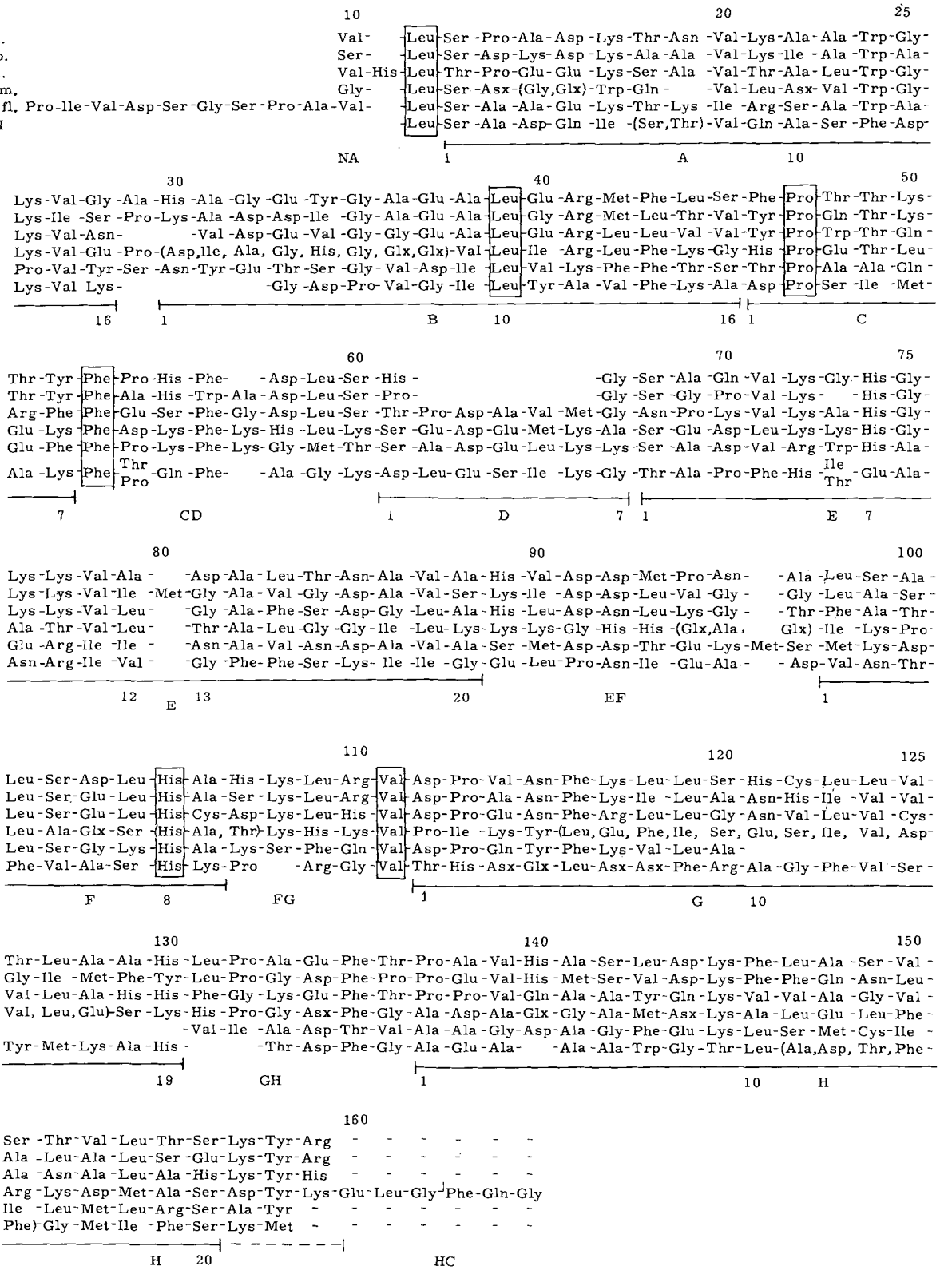
Fig. 1. Ontogeny of human hemoglobins (after *Betke* (ref. [77])).

The globin of the closely related lampern *(Lampetra fluviatilis)* consists of a sequence of 146 amino acids, whose homology with the above hemoglobins is more difficult to establish (see Table 1). The sequence begins with nine residues for which there is no counterpart in other hemoglobins. The molecule is shortened in the C-terminal region, where deletions of up to 10 amino acids have occurred[20]. The numerous monomeric and dimeric hemoglobins of the insect *Chironomus thummi* differ even more. They dissolve freely in the hemolymph of the aquatic larvae. This hemoglobin, which is the only invertebrate hemoglobin to be studied so far, has a peptide chain of only 136 amino acids. The deletions are in the N- and C-terminal parts of the chain[21].

Whereas the hemoglobins and myoglobins known so far of vertebrates have seven amino acids in corresponding positions, this number falls to three or four on comparison with insect hemoglobin. Thus nature achieves the same object here with an entirely different set of structural components. Despite the marked differences from vertebrate sequences, however, a similarity, particularly in the N-terminal region, cannot be overlooked. This justifies the notation used in Table 1 as an expression of a distant phylogenetic relationship. It is surprising to find that the Trp sequence (A 10—15), which is known from the investigations on vertebrates, has been displaced here into the C-terminal region of the chain (H 5—10)[22]. *Chironomus* hemoglobins also contain no cysteine.

The invariant residues in vertebrates include tryptophan A12, which forms another hydrophobic nucleus of the molecule besides the heme, glycine B6, which is the only amino acid that can be placed between the B helix and the superimposed D helix because of the absence of a side chain, proline C2, which forms the corner for the transition into the C helix, phenylalanine CD1 in close π-bond contact with

Table 1. Homologous alignment of the peptide chains of some hemoglobins. α-Hum, β-Hum: peptide chains of human Hb A [7]; α-Carp: α-chain of carp HB [71]; Mb-Hum: human myoglobin [14]; Lamp. fl.: *Lampetra fluviatilis* Hb [20]; CTT III: component III of the hemoglobins of *Chironomus th. th.* [21]. The six residues that agree in their arrangement in these peptide chains are enclosed in a box. NA – A – B ... HC— helical (underlined) and interhelical regions.



the heme, histidine E7, the distal heme contact, to which a functional significance was originally assigned, histidine F8, the proximal heme linkage, and tyrosine HC2, which is necessary for the attachment of the H helix to the molecule and for the allosterism of the tetrameric hemoglobin (see Section 3.2). Substitutions of Trp A12, Gly B6, His E7, and Tyr HC2 in insect hemoglobin show that the development has followed different paths in this case. Amino acids such as Val NA1α and His HC3 β which are important to the pH-dependent binding of O_2 in mammalian hemoglobins (Bohr effect), are deleted. This monomeric hemoglobin nevertheless shows a distinct pH dependence of the binding of O_2. The greatest Bohr effect measured so far is in fact found for dimeric components of these larval hemoglobins[23].

2.3. Evolution and Polymorphism of the Globins

The difference in the globin sequences of different species of animals corresponds to the degree to which the carriers are related. This was first recognized by *Zuckerkandl* and *Pauling*[24] on comparison of the sequences of the α chains of horses and of man, which differ in 18 positions. If one assumes similar rates of substitution of the hemoglobins for the two species since their divergence from a common ancestor some 90×10^6 years ago, the α chains of both species have diverged by an average of nine amino acids from the α-chain of the common ancestor. In other words, an average of one amino acid has been exchanged every 10×10^6 years.

The development of this fundamental idea has led in recent years to the systematic comparison of the primary structures of homologous proteins as a means of tracing the phylogeny of the species. Comparative morphology has already thrown considerable light on this topic, but this new method offers a number of obvious advantages:

1. The exchange of an amino acid follows from the alteration of a base in a codon of the DNA. This point mutation is the smallest genetically possible change, *i.e.* the "unit" of evolution (mutation and selection). It can thus be quantified, the data obtained being collected and evaluated by computers.
2. The sequence of the common ancestor can be deduced from a comparison of several sequences. Unlike most fossils, these structures characterize the exact phylogenetic branching points.
3. Comparative studies can in principle be applied to all proteins; the total quantity of information obtainable is therefore greater than by the use of the relatively rough morphological criteria.
4. It has been found that the rate at which amino acids are exchanged varies from protein to protein. The phylogeny can therefore be traced over very long periods (up to 3×10^9 years; phylum formation) in a protein with a low substitution rate, and over shorter periods (species formation) in another protein with a high substitution rate. Hemoglobin is a protein with a medium time scale.

The prerequisites for such studies, such as criteria of homology and convergence, influence of the generation and mutation rates, and gene duplication and deletion, are being discussed at present[25]. Moreover, no answer has yet been found to the question whether different amino acid sequences of a protein result from mutation and selection or mainly from mutation alone[26]. Gene duplications result in an increase in genetic material, which leads in turn to the development of proteins with new functions[70]. According to *Ingram* a primitive hemoglobin gene existed in the hereditary material of the animal kingdom, but it was only with the development of higher vertebrates that gene duplications allowed differentiation into the β type of chain (β—ε) and the α chain. The progressive shortening of these polypeptides in relation to myoglobin points to the increasing specialization to the subunits of a cooperative tetramer (see Section 3.2).

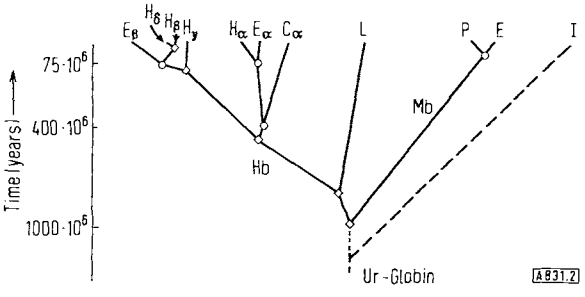


Fig. 2. Phylogenetic tree of the globins (modified after *Dayhoff et al.* [19]). α, β, γ, and δ peptide chains of man (H), horse (E), carp (C), lampern (L), sperm whale (P), and *Chironomus* th. (I) are shown. Hb = hemoglobin, Mb = myoglobin. Rectangles at the branching points indicate duplications of the globin genes, while circles indicate the development within chain types, which is shown for only a few examples for the sake of clarity. The time scale is provisional.

Figure 2 shows a phylogenetic tree deduced from a few very different globin sequences[19]. At least one gene is the carrier of information for one peptide chain. At least six globin-synthesizing genes must therefore occur in man. Investigations on Hb F, in which a whole-number relationship was found for a particular amino acid exchange[27], led the authors to conclude that there are at least two genes of a γ-chain synthesizing type. It was possible to verify by hybridization experiments with mice that this kind of ambiguity is not due to errors in protein biosynthesis[28]. It must therefore be assumed that even more than six genes contain the hemoglobin information, and under certain conditions they put it into effect. This is also confirmed by the observation that anemic goats synthesize an additional hemoglobin that strongly binds O_2[29]. The most pronounced polymorphism of a hemoglobin is found in *Chironomus* larvae, from whose hemolymph at least twelve components can be separated by chromatography and electrophoresis; exchange of neutral amino acids and variations of the length of the peptide chain in homogeneous fractions have also been described[21]. The diversity of these structures makes them suitable subjects for comparative investigations by physicochemical methods. This also offers a possible explanation for the discrepancy between the number of proteins synthesized by a higher organism and the very much greater information capacity of its DNA.

The methods of sequence analysis are suitable for the detection of small differences in primary structures only if used very carefully. The capabilities of present-day protein separation methods are also overtaxed. An important advance may result from the automation of Edman degradation[30]. Further sequences, even of high molecular weight hemoglobins[31], should become known during the next few years, and microheterogeneities should be found in sequences that are already familiar.

The covalent structure of a protein as formed by biosynthesis contains the information for the three-dimensional folding and function of the molecule. If this proposition is accepted, the way is open to a genetic understanding of a protein as a product of a long evolution process involving mutation and selective adaptation; at the same time, one is faced with the task of reading the properties of these substances from their primary structures. This aim is still far beyond the capabilities of theoretical chemistry at present. Once it has been attained, it will be possible (provided that proteins can be synthesized) to use the unsurpassed activities of the biocatalysts for other purposes, *e.g.* in chemical technology and medicine. Thus in addition to its phylogenetic importance, the comparative investigation of primary structures, particularly in the variable hemoglobin, also has a purpose connected with theoretical chemistry; it shows the variety of ways in which the structural units of a protein can be fitted together without appreciably changing the basic function or the conformation. It looks as if the comparative analysis of hemologous sequences could lead to the discovery of hitherto unknown rules of protein structure.

2.4. Abnormal Hemoglobins

The above-mentioned primary structure of hemoglobin A is normally found for all human beings, irrespective of race. It is common to the human population of the earth, and even the hemoglobin of chimpanzees is identical in structure. Deviations from this structure are described as abnormal hemoglobins; they are frequently responsible for diseases. Since the identification of the anomaly of sickle cell hemoglobin (HbS) as amino acid exchange ($\alpha_2\beta_2$6Glu→Val) by combined electrophoresis and partition chromatography of the tryptic peptides (fingerprint) of HbS and HbA[8], more than one hundred other anomalies have now been reported[32]. Their explanation by inheritable point mutations and (in the case of deletions) nonhomologous crossing over of the DNA (exchange of fragments) is generally accepted, though not yet accessible to direct investigation. A significant proportion of 2217 possible one-point mutations[25] has thus been described after only a few systematic investigations. The other mutations may also be expected to be found in the course of time, insofar as they are compatible with life. It was calculated from these investigations that an average of one human being in every 600 has an abnormal hemoglobin. Table 2 shows some examples that particularly contribute to our understanding of the function of the molecule (see also Section 3.3). If one examines the entire list of these changes, one finds that the exchanged residues usually differ in their charge. This is in part due to the investigation method, *i.e.* electrophoresis; the exchange of neutral residues is difficult to detect. In addition to exchanges, deletions of one or more amino acid residues have been described, as in Freiburg and Gun Hill hemoglobins, and hybridization of the β and δ chains[13] has been found in Lepore hemoglobin.

Table 2. Some abnormal hemoglobins (see also Section 3.3).

Type	Position	Exchange
Freiburg	βB5 (23)	Val → 0
E	βB'8 (26)	Glu → Lys
Genf	βB10 (28)	Leu → Cys
Philly	βC1 (35)	Tyr → Phe
Hammersmith	βCD1 (42)	Phe → Ser
Turin	αCD1 (43)	Phe → Val
M Boston	αE7 (58	His → Tyr
M Saskatoon	βE7 (63)	His → Tyr
Zürich	βE7 (63)	His → Arg
M Milwaukee	βE11 (67)	Val → Glu
Sydney	βE11 (67)	Val → Ala
M Iwate	αF8 (87)	His → Tyr
M Hyde Park	βF8 (92)	His → Tyr
J Cape Town	αFb4 (92)	Arg → Glu
Chesapeake	αFb4 (92)	Arg → Leu
Gun Hill	βF7–FG4 (91–97)	there 5 residues → 0 Lys, His, Asp, Cys, Leu deleted
Köln	βFG5 (98)	Val → Met
Kansas	βG4 (102)	Asn → Thr
Hiroshima	βH21 (143)	His → Asp
Rainier	βHC2 (145)	Tyr → His

3. Three-Dimensional Structures and Functions

3.1. Tertiary Structure

Our knowledge of the secondary, tertiary, and quaternary structures of hemoglobin and other proteins comes mainly from X-ray analysis.

The X-ray analysis of sperm-whale myoglobin[5], first showed the three-dimensional structure of this type of molecule. More than 70% of the globular protein has a helical structure, which is divided into eight regions (A, B,...H) (secondary structure); the chain is folded in a characteristic manner around the heme (Fig. 3a). Contact is made with the heme through a nitrogen atom of the imidazole side chain of His F 8 (5th coordination site of the heme Fe^{2+}), by polar bonds from the protein to the propionic acid residues of the heme, and above all by van der Waals forces (hydrophobic interactions) with the inward-facing lipophilic amino acid residues of the protein. The tightly packed hydrophobic nucleus is shielded from the surrounding water and kept in solution by hydrophilic side chains. The sixth coordination site of Fe^{2+} is occupied by O_2 in the oxygenated state (HbO_2), and is free in the deoxygenated state (Hb). If the iron of heme is oxidized (Fe^{3+}), the molecule can no longer function; the sixth coordination site is now occupied by water, which forms a hydrogen bond to the histidine E 7.

The subunits of hemoglobin (α, β chains) (Fig. 3b)[6], *Chironomus* hemoglobin, and the hemoglobins of *Glycera di-*

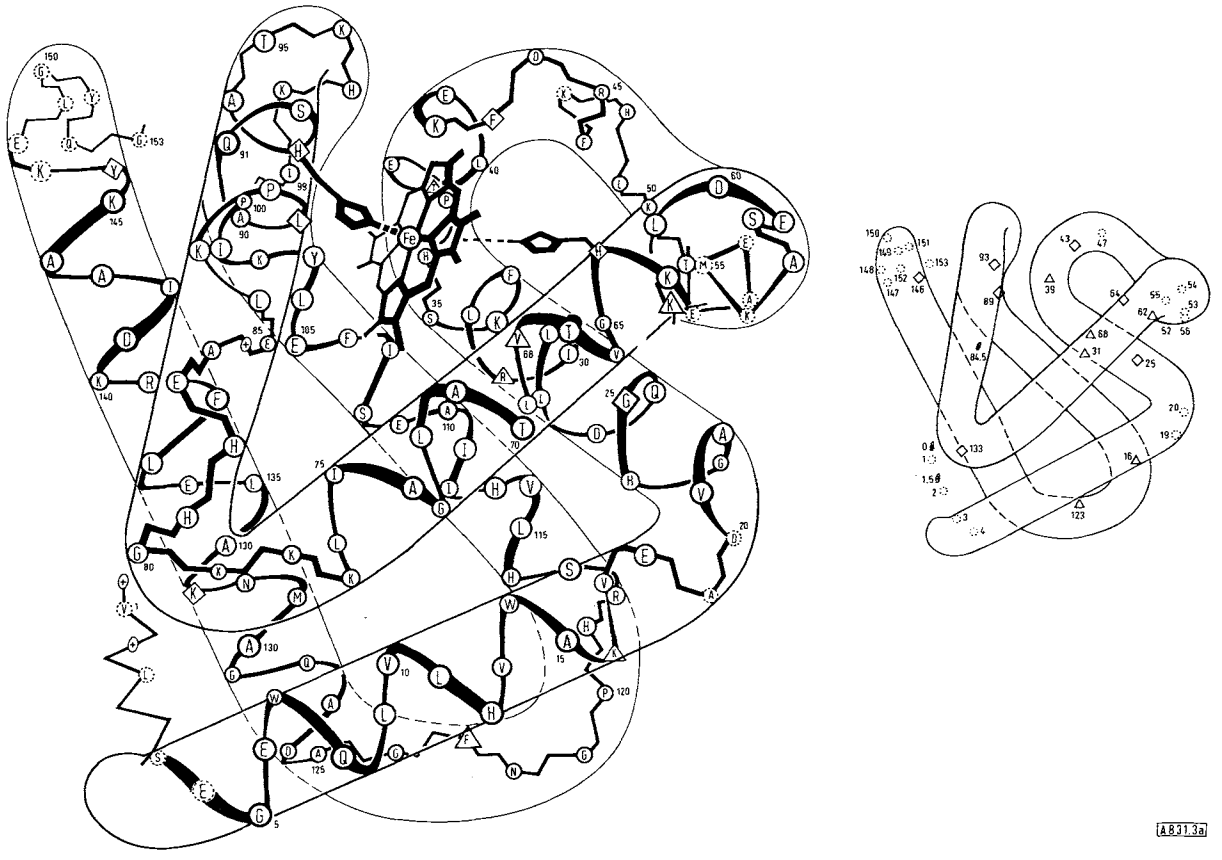


Fig. 3a. Conformation scheme of sperm-whale myoglobin (after *Dickerson* from *Dayhoff et al.* [19]). The amino acids are denoted by their single-letter symbols. In the small drawing, △ indicates invariant residues in vertebrate globins except that of *Lampetra fluviatilis*, ○ denotes residues that are deleted in some vertebrate globins, ◇ means invariant in all vertebrate globins, and ⊕ denotes insertions.

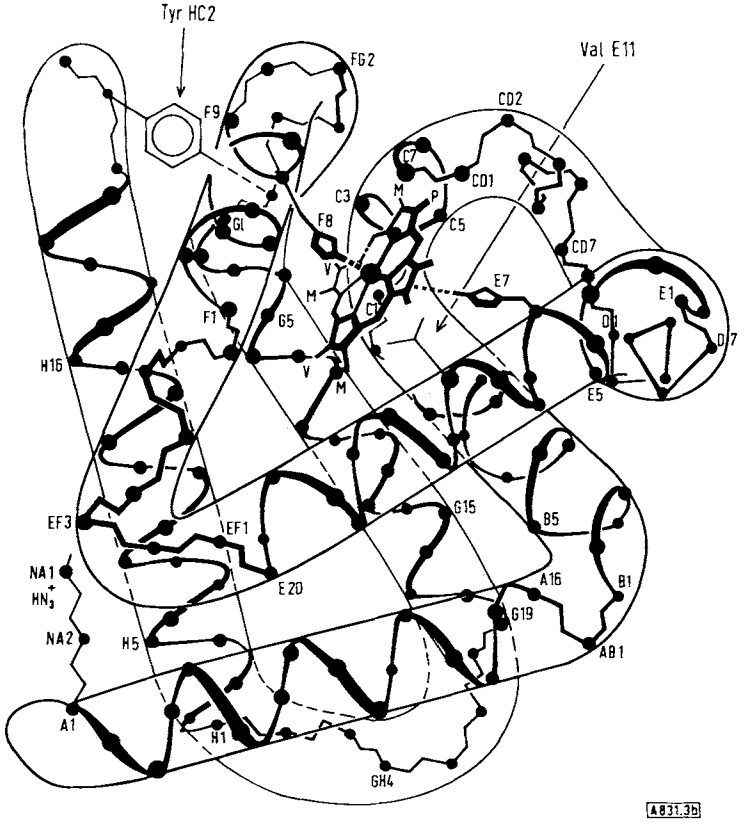


Fig. 3b. Conformation scheme of the β chain of HbA; helical positions and the position of Tyr HC2 are shown (after *Perutz* [64]).

branchiata and *Petromyzon marinus*[34], *i.e.* all the hemoglobins or their subunits on which X-ray studies have been carried out, have a tertiary structure similar to that of myoglobin. Slight deviations are found, such as those that can sometimes be deduced from the examination of the homologous primary structures. The α chain cannot form a D helix because of deletions D 2—6, and both the α and the β type are shortened at the carboxyl end in comparison with myoglobin. Insect hemoglobin exhibits further shortenings; thus one turn of the B helix is missing. The result is that the A helix bends at Phe A 12 and approaches closer to the center of the molecule. CD measurements show how this correction is facilitated by the shortening of the residue A 12 Trp→Phe[35]. The H helix is disturbed by a deletion and bent, while the carboxyl end exhibits a different construction with Met, corresponding to the absence of Tyr H 22 (≙ HC 2 of the α, β chains)[33].

The changes found here are the most pronounced of all those found for hemoglobin tertiary structures. However, though this molecule has little resemblance in its primary structure to the hemoglobin or myoglobin of mammals, the construction of a protein that reversibly binds O_2 is still the same, despite a phylogenetic distance of probably more than 10^9 years. This is true in particular of the general arrangement of the apolar heme contacts, *e.g.* the phenylalanine CD 1, and of the proximal bonding site of the heme iron His F 8. The distal histidine E 7 appears to be a develop-

ment of the vertebrates but its significance becomes somewhat unclear on comparison with the structure of insect hemoglobin. However, the sixth coordination position of the Fe^{2+} seems more readily accessible here, and this may explain the change in the kinetics of ligand binding and of autoxidation[36]. Details of the X-ray structures of *Glycera* and *Petromyzon* hemoglobins have not yet been published.

An interesting addition to the investigations just mentioned is the neutron-diffraction analysis of sperm-whale myoglobin crystallized from a D_2O solution containing ammonium sulfate[38]. The result agrees well with the X-ray findings, apart from the positions of a few amino acid side chains.

3.2. Quaternary Structure and Function

While the investigation of the monomeric hemoglobins was very difficult, the study of the quaternary structure, *i.e.* the noncovalent bonding (hydrophobic interactions, ionic interactions, and hydrogen bonds) of the subunits to form the tetrameric functional unit of vertebrate hemoglobins, was even more so. A regulating organization of this nature is found for many enzymes, and the possibility of studying it in hemoglobin led to the designation of the latter as an "honary enzyme".

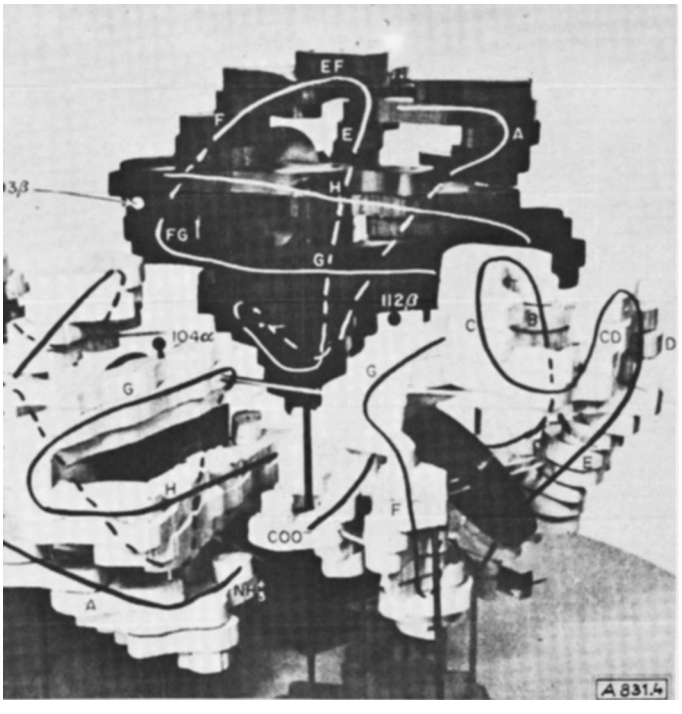


Fig. 4. Structure of hemoglobin according to 5.5 Å X-ray studies (from *Muirhead et al.* [37]). The subunits are parted from one another for clarity, the course of the peptide chain is shown, and a β chain in the foreground of the picture has been removed.

The association of the four subunits of vertebrate hemoglobin is easily influenced. Experiments cannot usually be carried out on hemoglobin in a concentration corresponding to that in the erythrocytes. In fact, the conditions that must be used are often such that the hemoglobin is already largely split into dimers or monomers. It is difficult to make accurate allowance for this situation, since the dissociation of hemoglobin has not yet been conclusively explained.

The dissociation is symmetrical, *i.e.* hemoglobin consisting of two α and two β chains gives two subunits containing one α and one β chain each. It should be noted that $\alpha_1\beta_1$ and $\alpha_2\beta_2$ or $\alpha_1\beta_2$ and $\alpha_2\beta_1$ dimers[*] could in principle be formed (see Fig. 4). The $\alpha_1\beta_1$ ($\alpha_2\beta_2$) contact involves 34 amino acids with about 110 hydrophobic bonds (distance between hydrophobic groups <4 Å), while the $\alpha_1\beta_2$ ($\alpha_2\beta_1$) contact involves 19 amino acids (80 atomic contacts)[37]. The dissociation into dimers probably takes place at the $\alpha_1\beta_2$ contact, *i.e.* it leads to $\alpha_1\beta_1$ ($\alpha_2\beta_2$) dimers[39,43]. Recent studies on hybrid hemoglobins using isoelectric focusing show that this symmetrical cleavage takes place in the same manner in ligand-free hemoglobin as in hemoglobin with ligands (HbO_2, HbCO, $HbFe^{3+}CN^-$, *etc.*)[40].

An $\alpha_1\beta_2$ dimer should not bind two ligands independently[41], since the contact that transmits the interaction of the two bonding sites is retained[42]. If one attempts to summarize the results that have been obtained so far for HbA, one finds the following: HbO_2 (or hemoglobin with other ligands) dissociates into dimers, and probably partly into monomers, in solutions with high salt concentrations (1.0 to 2.0 mole/l of NaCl) and in acidic ($pH<4.7$) and alkaline solutions ($pH>9.0$). Ligand-free hemoglobin dissociates to a much smaller extent[44–46]. Complete dissociation into monomers is difficult, but can be achieved if the SH groups are blocked with *p*-chloromercuribenzoate (pMB). This technique of isolating native subunits of HbA *via* the pMB derivatives[47] was expected to yield information on differences in the functions of the α and β chains. Though numerous investigations have been carried out by many research groups with the aid of methods such as ultracentrifugation, membrane osmometry, and gel filtration, the results as a whole are still unsatisfactory. This may be partly due to the difficulty of producing comparable preparations.

The aim of the physicochemical studies on hemoglobin is mainly to clarify the problem of the regulated binding of oxygen. To bind the four ligands (4 O_2, 4 CO, *etc.*) on the hemes, all four bonding sites must act together (homotropic interaction). This process has also been referred to inaccurately as heme-heme interaction. However, the shortest distance between two heme iron atoms ($\alpha_1-\beta_2$) is 25 Å, so that no direct interaction between them is possible; on the contrary, the interaction occurs indirectly through changes in the conformation of the protein (allosterism). Starting with the hyperbolic oxygen-binding curve of myoglobin and the sigmoid course of this curve for hemoglobin[48] (see also Fig. 7), it is necessary not only to describe the nature of the reversible binding of the O_2 molecule to the sixth coordination site of the heme iron, but also to gain an understanding of the manner in which the subunits work together in hemoglobin (cooperative binding of O_2), for which the sigmoid binding curve is

[*] The subscripts 1 and 2 are used here to distinguish the two α or β chains.

characteristic. It is also necessary to explain the Bohr effect (release of protons on binding of oxygen) and the decrease in oxygen affinity on stoichiometric bonding of polyphosphates, particularly 2,3-diphosphoglyceric acid (2,3-DPG), which is present in high concentrations in the erythrocytes[49].

Hemoglobin is also responsible for about 60% of the transport of the metabolic end product CO_2 back to the lungs; the carbon dioxide reacts with the N-terminal NH_2 groups to form the carbamate[50].

$$R^1{-}NH_3^+ \rightleftharpoons R^1{-}NH_2 + H^+$$
$$R^1{-}NH_2 + CO_2 \rightleftharpoons R^1{-}NH{-}COO^-H^+$$

Protons are released both in the binding of CO_2 and in the uptake of oxygen. The reaction with H^+, 2,3-DPG, or other (poly)phosphates, and probably also CO_2, thus depends on the binding of O_2. The protein intervenes here between different bonding sites (heterotropic interaction). These substances may be called allosteric effectors. They all have an affinity for ligand-free hemoglobin. Myoglobin behaves differently, and the insect hemoglobins occupy an intermediate position. The reaction

$$Hb + 4\,O_2 \rightleftharpoons Hb(O_2)_4$$

is empirically described by the Hill equation

$$Y = Kp^n/(1 + Kp^n)$$

where Y is the percentage saturation of the Hb with oxygen and p is the partial pressure of O_2.

The Hill coefficient n has a value of 1 for myoglobin and for isolated α and β chains[51]; if cooperativity of the four bonding sites is complete, n can theoretically be 4; its value for human hemoglobin is 2.8.

An investigation of the kinetics of ligand binding theoretically requires the determination of eight rate constants[52] from one reaction course on the basis of a simple scheme in which only the binding of four ligands to four bonding sites is considered. This is not possible at present. Two simplified kinetic models have been developed to describe the cooperative binding[53, 54]. However, both the "concerted" reaction mechanism, which describes the transformation of the quaternary structure as an "all or nothing" reaction, and the sequential course, in which the change in the quaternary structure results from a sequence of interdependent changes in the conformation of the subunits (induced fit), agree only in part with the results reported so far. By kinetic studies using temperature and field jump methods, it is possible to resolve the complex process into a few relaxation components, which are assigned to the binding of O_2 and to intermolecular and intramolecular changes in conformation[55].

A significant contribution to this problem was made by *Gibson* and *Parkhurst*[56]. These authors made use of the ability of HbCO to dissociate for a short time into Hb and CO on exposure to light. The Hb molecule (or some subunits) is then free from ligands, though its conformation is still the same as in HbCO. Differences can be detected in the binding of the ligands by means of such investigations. The dissociation and binding of the first three ligands are the rate-determining steps of the homotropic interaction.

ORD and CD studies[57] show that both the binding of O_2 and the association of the subunits are accompanied by changes in the conformation of the molecule[58]. On the whole, α and β chains differ from hemoglobin in their properties. pH-dependent conformational changes have also been observed in monomeric and dimeric insect hemoglobins[59]. Deoxygenated hemoglobin, unlike all other forms with bivalent or trivalent iron (in which water or other ligands such as CN^- are bound), is ligand-free. The bonding state of the heme iron can be established with the aid of magnetochemical methods and ESR spectroscopy[60]. The introduction of spin labeling at certain bonding sites in the globin, *e.g.* on Cys(93)β, also allows the observation of changes in the conformation of the subunits on binding of O_2[61].

X-ray[62] and Mössbauer spectroscopic studies[63] decide the question of the bonding of an O_2 molecule to the Fe^{2+} in favor of *Pauling*'s model. The oxygen molecule forms an angle of 120° with the plane of the heme. Investigations on forms of the iron complex with and without ligands and on model substances indicate that in deoxyhemoglobin, the central iron atom has moved about 0.8 Å out of the plane of the heme toward F 8[64]. In the oxy form, on the other hand, it lies in the plane of the heme. Monomeric deoxy-Hb and HbCO from *Chironomus* show a displacement of only 0.2 Å for the Fe^{2+} in relation to the heme[65].

Important contributions to the elucidation of allosterism on the molecular level, the Bohr effect, and the action of 2,3-DPG have been made by X-ray analysis. The comparative 5.5 Å resolution of equine oxyhemoglobin and human deoxyhemoglobin published by *Perutz et al.* in 1967 showed that the oxygenation of the molecule leads to reorientation of the subunits such that the distance between the Fe atoms of the heme groups $\beta_1\beta_2$ is changed by almost 7 Å, and the contacts on $\alpha_1-\beta_2$ and $\beta_1-\alpha_2$ assume a new steric orientation[37]. No change in the tertiary structure was observable in the 5.5 Å resolution, though logic demands such a change. It was only with 2.8 Å resolution that sufficient details were obtained for a description of the steric course of the change in conformation[64]. The rupture of intramolecular salt bridges plays an important energetic role here (the total change in the free energy ΔG^0 of hemoglobin on oxygen uptake is 10—12 kcal/mole).

The process starts with the movement of the central iron atom into the plane of the heme ring, which occurs on oxygen uptake. This movement is transmitted to the proximal His F 8, with the result that the F helix is drawn into the interior of the molecule and approaches the H helix (Fig. 5). The tyrosine HC 2, which is invariant for all vertebrates, is essential to the subsequent change in the conformation of the subunits. The side chain of this amino acid forms a hydrogen bond to the amide nitrogen of Val FG 5 in deoxyhemoglobin, and the hydrophobic ring of Tyr is enclosed in apolar fashion by the H and F helices. This anchoring of the C-terminal part of the H helix is rendered impossible by the approach of the F helix; Tyr is forced

out of its position, the C-terminal part of the H helix becomes free, and the salt bridges from the C-terminal residues of the α and β chains are opened. The bonds between the α-carboxyl groups of Arg HC 3 (141) α_1 and the amino group of Val NA 1 (1) α_2 and between the guanidinium

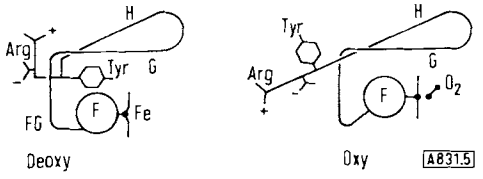


Fig. 5. Scheme of the change in structure of a subunit of hemoglobin on O_2 uptake (after *Perutz* [64]).

ion of the same arginine and the β-carboxyl group of the aspartic acid in H 9 (126) α_2 are broken; the linkage between the α-carboxyl group of His HC 3 (146) β_1 and the ε-amino group of Lys C 5 (40) α_2 and the salt bridge from the imidazolium ring of His HC 3 to the β-carboxyl group of Asp FG 1 (94) β_1 are also broken. The ionic interactions between 2,3-DPG in the hydrophilic central cavity of the tetrameric hemoglobin molecule and side chains of the β chains (Val NA 1 (1), Lys EF 6 (82), His H 21 (143)) become unstable on transition to oxygenated hemoglobin.

Evidence supporting the assumption that the C-terminal amino acids of the α and β chains and the bonding of the 2,3-DPG are important to the conformation of the hemoglobin and hence to the binding of oxygen can be seen in the facts that removal of the histidine and the arginine reduces the Hill coefficient to $n \simeq 1$ and that removal of histidines and of Val NA 1 α are changed to such a degree that 0.7 proton dissociates from the molecule per heme ligand[66].

Since binding of the ligand oxygen to heme iron is easier in the case of the α chains than in the case of the β chains on purely steric grounds, it may be assumed that oxygenation of the two α chains of the molecule occurs first. These subunits are accordingly changed as described above from the conformation of the deoxygenated molecules into that of the oxygenated molecules. The change in the conformation of some subunits increases the readiness of the entire molecule to undergo a change in its quaternary structure. The subsequent reorientation of the β chains facilitates the access of the oxygen to their iron atoms, and the entire molecule, charged with four molecules of oxygen, will now be in the form of oxygenated hemoglobin (Fig. 6). This reaction course contains elements from both of the models mentioned above. The details of the reaction may differ with the medium, but the steric mechanisms should remain unchanged. Moreover there is no indication that these data, which were established for crystals, are not also valid for the dissolved protein.

The fundamental value of this method to the functional analysis of proteins can be deduced from the fact that X-ray analysis allows the detection of fine details of the molecular structure and even the interpretation of their importance to dynamic processes. On the other hand, there is a need for other, complementary methods that directly determine the dynamic parameters of proteins in solution, and which do not stop with an overall examination of the molecules, but again continue to probe down

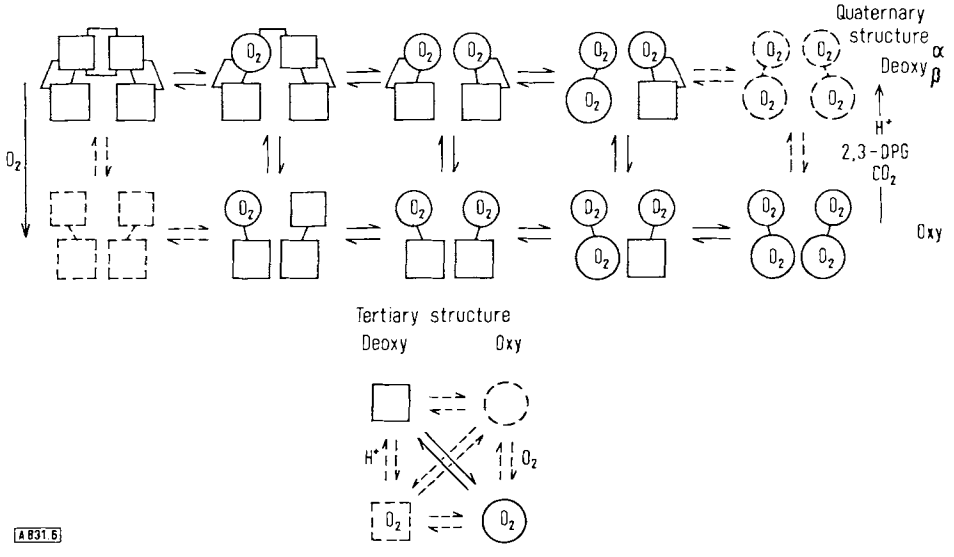


Fig. 6. Scheme of the change in the conformation of hemoglobin on conversion into HbO_2; quaternary structure and tertiary structure (after *Perutz* [64]).

the 2,3-DPG increases the oxygen affinity of the hemoglobin. Removal of the C-terminal histidine of the β chain also causes the Bohr effect to be halved[73]. Blockage of the N-terminal Val NA 1 has a similar effect[50].

The liberation of H^+ results from the approach of the His HC 3 (146) β and probably also the His H 5 (122) α to negative and positive groups in the deoxygenated and oxygenated states respectively. The pK values of these

to atomic dimensions. The results that have recently been achieved with high-resolution NMR spectroscopy are very promising. Signals due to individual amino acid side chains, particularly those of the functionally important histidines, have been identified, and the first steps of a detailed analysis have been taken. Interpretation of the results is again facilitated by comparison of hemoglobins having different primary structures and in various bonding states[67, 68].

3.3. Functional Abnormalities of Hemoglobin

It is fascinating to try to understand the abnormalities of some hemoglobins on the basis of the X-ray model[69]. Only a few examples can be chosen here from the large amount of available data. A number of general results emerge:

a) The exchange of polar residues on the surface of the molecule (in heterozygotes) is not usually accompanied by clinical symptoms, *e.g.* with $HbI_{Toronto}$ α A 3 (5) Ala →Asp; $HbE_{Saskatoon}$ β B 4 (22) Glu→Lys.

b) Practically any alteration of nonpolar side chains in the interior of the molecule leads to losses of ability to function and of stability; this is particularly true of the environment of the heme (60 atomic contacts): Hb_{Turin} α CD 1 (43) Phe →Val loses two CH contacts on the heme, and is unstable. The situation is worse in the case of $Hb_{Hammersmith}$ β CD 1(42) Phe→Ser, in which a polar side chain is introduced in addition to the loss of the two hydrophobic contacts; water enters the heme pocket, and heme is split off.

c) Exchange of amino acids at the contacts of the subunits and the N and C ends affects the function (allosterism, Bohr effect, O_2 affinity, *etc.*) and the dissociation into subunits. Changes in the $\alpha_1\beta_1$ ($\alpha_2\beta_2$) contact, *e.g.* HbE β B 8 (26) Glu→Lys, generally have no effect on the interaction of the subunits, unlike changes in the $\alpha_1\beta_2$ ($\alpha_2\beta_1$) contact, *e.g.* $Hb_{Chesapeake}$ α FG 4 (92) Arg→Leu with reduced interaction and increased O_2 affinity. However, this hemoglobin still has a Bohr effect, which is further reduced in the case of $Hb_{Hiroshima}$ β H 21 (143) His→Asp (Fig. 7).

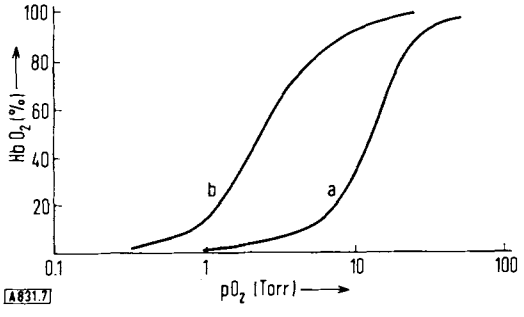


Fig. 7. O_2 binding curves of HbA (a) and of $Hb_{Hiroshima}$ (b) at pH = 7.4 in 0.1 mole/l phosphate buffer and at 20 °C (after *Imai* (ref. [72])

d) A special group is formed by the Hb M types, in which the properties of the bonding site are changed to such a degree that heme iron is in the form of Fe^{3+} (methemoglobin) and does not bind O_2. $Hb_{Milwaukee}$ β E 11 (67) Val→Glu forms an ionic bond with the iron and stabilizes it as Fe^{3+}. Replacement of the distal His E 7 or of the proximal His F 8 by Tyr in the α or β chains leads in all four possible cases to oxidation to Fe^{3+} and consequent loss of ability to bind O_2. Ionic bonds to the Fe^{3+} are presumably also formed in this case. In $Hb_{Zürich}$ β F 8 (92) His→Arg, on the other hand, the distal His is again substituted, but the function is not greatly impaired; this is not a Met-Hb. Arginine does not fit into the heme pocket, and it therefore projects into the solution. It is found here that the distal side chain is not absolutely necessary for the reversible binding of O_2. This agrees with the findings for insect hemoglobin.

It is impossible to grasp in detail the effects, on the molecular level, of every exchange of an amino acid, and precise functional testing is only rarely possible. It would be useful to examine these anomalies systematically and to collect blood conserves of their carriers for medical and scientific purposes. Here again, investigations on the red blood pigment could point the way for the study of molecular defects in other proteins, which will undoubtedly be discovered in the next few years.

Causal therapy of these morbid changes is not possible at present.

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Pulse Fourier Transform ^{13}C-NMR Spectroscopy, Principles and Applications[**]

By Eberhard Breitmaier, Günther Jung, and Wolfgang Voelter[*]

As a result of the development of pulse Fourier transform NMR *spectroscopy,* ^{13}C *resonance has become accepted as a means of elucidating the structures of organic compounds having the natural* ^{13}C *abundance. Assignment of the signals is facilitated by broad-band and off-resonance proton decoupling and by knowledge of longitudinal relaxation times. The pulse Fourier technique, which is more sensitive and faster than conventional* NMR *spectroscopy because of multichannel excitation, allows* ^{13}C *measurements within a short time even on dilute samples of high molecular weight compounds without prior enrichment in* ^{13}C.

1. Introduction

The chemical shifts and coupling constants of protons provides such conclusive information about the structures of many organic compounds that proton resonance has grown into one of the most important routine methods of instrumental analysis available to the organic chemist. However, its usefulness is limited for two reasons: Firstly, the center of interest in organic chemistry is not the protons but the carbon skeleton. Thus the physical properties and reactivity of organic compounds are explained by the bonding states of the carbon atoms that can be calculated approximately by quantum-mechanics. Secondly, numerous organic molecules contain too few magnetically nonequivalent protons, so that ^{1}H-NMR spectroscopy provides little or no information about the carbon skeletons of such compounds. The obvious solution is to try to use the magnetic isotope ^{13}C, with nuclear spin 1/2, as a probe for NMR spectroscopy of organic compounds.

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2. Problems of ^{13}C-NMR Spectroscopy

The isotope ^{13}C requires much longer times for longitudinal relaxation than the proton, with the result that flipping of the spin states on irradation at radio frequencies is much slower. Moreover, the abundance of ^{13}C in natural carbon is only 1.1%, so that large samples are necessary for the observation of ^{13}C resonance. Finally, ^{13}C resonance is much less sensitive (1.59%) than ^{1}H resonance (100%) at the same magnetic field strength, because of the small gyromagnetic ratio of ^{13}C.

In addition to these fundamental difficulties, routine ^{13}C-NMR spectroscopy has until now also been hindered by instrumental difficulties. Conventional high-resolution NMR spectrometers record the NMR spectra with continuous change of frequency or of magnetic field over the Larmor frequency range of the observed nucleus. Only a narrow frequency band contributes to the excitation of the resonances at any instant. The signal/noise ratio (S/N), which serves as a measure of sensitivity, is consequently low in this technique, which is described as the frequency sweep or field sweep method. The sensitivity can be improved by accumulation of spectra with averaging computers, the noise being averaged out by the CAT (Computer Averaged Transitions) process, since S/N increases with the number of scans n:

$$S/N \sim n$$

Even if the long times that this entails are acceptable, the long-term stability of conventional NMR instruments is usually too low to give a usable ^{13}C-NMR spectrum with long recording times for a saturated, but (because of low solubility) dilute solution of an organic compound.

These fundamental and instrumental difficulties have led to the development of the new recording technique known as pulse Fourier transform (PFT) NMR spectroscopy[1-3]. The basis of this technique is the free induction decay of the Bloch nuclear resonance theory[4, 5]. PFT NMR spectroscopy can be used for any magnetic nucleus. In particular, ^{13}C-NMR spectroscopy of organic compounds having the natural ^{13}C abundance has become a routine method of analysis as a result of the PFT technique.

3. Principles

3.1. The Bloch Nuclear Magnetic Resonance Theory

To observe the nuclear magnetic resonance, the sample is placed in a static magnetic field $\vec{H}_0$, and a radio-frequency field $\vec{H}_1$ is applied perpendicular to $\vec{H}_0$. If the frequency of the field $\vec{H}_1$ is equal to the Larmor frequency ν_L of the nucleus used as the probe, an absorption signal is recorded in the receiver of the NMR spectrometer. The Bloch theory[4, 5] explains the action of the fields $\vec{H}_0$ and $\vec{H}_1$. This theory describes the behavior, not of one nucleus, but of the macroscopic magnetization $\vec{M}$ of a collection of nuclei under the influence of $\vec{H}_0$ and $\vec{H}_1$.

Under the influence of the field $\vec{H}_0$ alone, the axes of rotation of the nuclei precess with an angle α about the direction of the field $\vec{H}_0$ (Fig. 1a). For a nucleus with spin $I=1/2$, this results in a highly populated orientation of low energy in the direction of the field $\vec{H}_0$ and a poorly populated orientation of high energy in the direction opposite to that of the field $\vec{H}_0$ (Fig. 1a; note the number of vectors). The resultant macroscopic magnetization M is thus parallel to the field $\vec{H}_0$ (Fig. 1a in the z direction), and causes a small, measurable nuclear susceptibility.

If the x, y, z coordinate system is considered as rotating about the z axis with the Larmor frequency ν_L, Figure 1a simplifies to Figure 1b, in which $\vec{M}$ rotates in the z axis with frequency ν_L. The radio-frequency field $\vec{H}_1$ with the Larmor frequency ν_L, when applied perpendicular to $\vec{H}_0$,

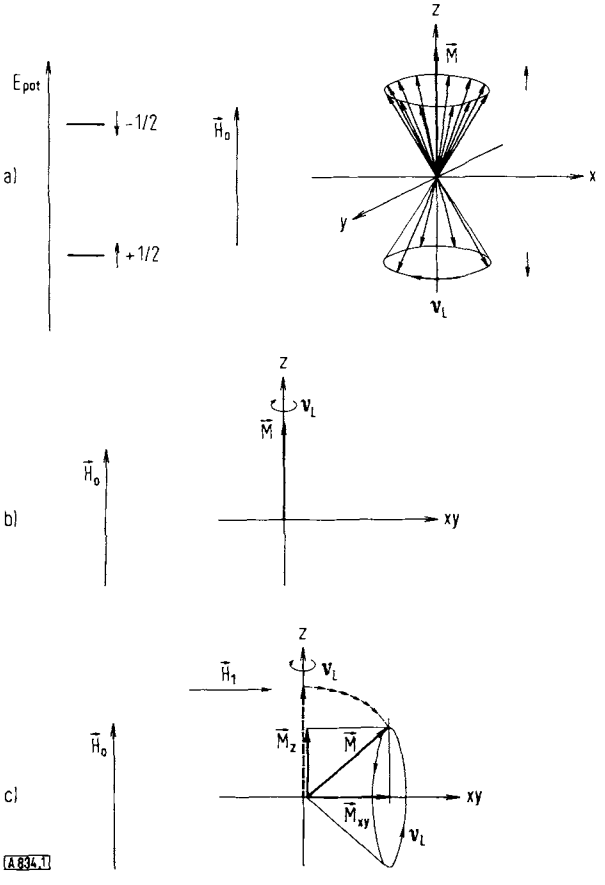


Fig. 1. a) Orientation of the nuclear spin in the field $\vec{H}_0$ and the resulting magnetization $\vec{M}$. b) The rotation of the system of coordinates about the z direction with the Larmor frequency ν_L simplifies a) to b). c) Action of the field $\vec{H}_1$ perpendicular to $\vec{H}_0$ on $\vec{M}$. (Fields $\vec{H}_1$ at 180° to $\vec{H}_0$ thus cause a complete inversion of the population of the spin levels.)

exerts a force on the vector of the macroscopic magnetization $\vec{M}$. The vector $\vec{M}$ escapes from this force by precessing about the direction of $\vec{H}_1$. $\vec{H}_1$ and $\vec{M}$ are in phase, and $\vec{M}$ has two components: $\vec{M}_z < \vec{M}$ in the z direction and $\vec{M}_{xy} < \vec{M}$ in the xy plane (Fig. 1c). The decrease in the magnetization in the z direction (longitudinal magnetization) is a result of resonance. If $\vec{H}_1$ oscillates with the Larmor frequency ν_L, some nuclei reverse their spin more or less rapidly, corresponding to their longitudinal relaxation time T_1. As they do so, they absorb energy from $\vec{H}_1$. The populations of the two orientations become practically equal, and the magnetization consequently decreases from $\vec{M}$ to $\vec{M}_z$.

3.2. Free Induction Decay

After the resonance, the transverse magnetization $\vec{M}_{xy}$ decays exponentially with the transverse relaxation time T_2, losing the phase coherence with the $\vec{H}_1$ field. This process is referred to as free induction decay (FID)[4, 5]. Since the transverse magnetization $\vec{M}_{xy}$ results from components due to the different Larmor frequencies of one kind of nuclei in a molecule, the FID contains all information of the NMR spectrum of that molecule.

Free induction decays are observable as "wiggles" at high resolution and rapid passage of many resonances (*e.g.* the ^{1}H signal of tetramethylsilane), though wiggles may also be caused by field inhomogeneities. Immediately after passing the resonance condition

$$\nu_{\vec{H}_1} = \nu_{\vec{M}_{xy}} = \nu_L$$

phase and frequency of $\vec{H}_1$ and $\vec{M}_{xy}$ are almost equal. The interference between $\vec{H}_1$ and $\vec{M}_{xy}$ is therefore a beat, which synchronously with the FID, decreases exponentially with T_2.

When the resonance condition has been passed, the vector of the longitudinal magnetization $\vec{M}$ reverts to the z direction exponentially with the longitudinal relaxation time T_1, that means time independent of the FID.

3.3. Pulse Interferograms

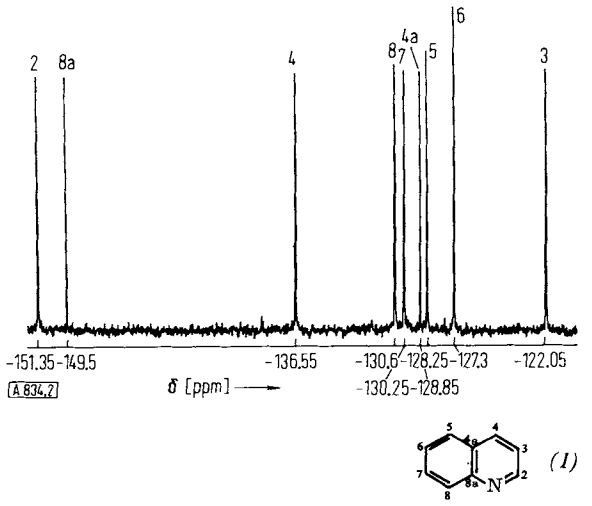
The beat interference signals of the FID can also be initiated by short (a few microseconds) radio-frequency pulses $\Delta\vec{H}_1$ applied at right angles to $\vec{H}_0$.

In pulse NMR spectroscopy, such a pulse encounters a molecule with n magnetically nonequivalent nuclei, *i.e.* n Larmor frequencies ν_L. Instead of one single FID beat interference, the receiver of the spectrometer then records the superimposed interferences of all the excited Larmor frequencies. If the frequency spectrum of the applied pulse is sufficiently large, all n Larmor frequencies of the molecule are excited. The resulting pulse interferogram, which represents the decay of the transverse magnetization $\vec{M}_{xy}$ as a function of time, (see Fig. 3a) thus contains all the information of an NMR spectrum obtained by frequency sweep or by field sweep (Section 2). The time required to register the interferogram is of the order of longitudinal relaxation times T_1[2], *i.e.* in the region of fractions of a second (^{1}H) or seconds (^{13}C).

4. PFT NMR Spectroscopy

4.1. Principle and Advantages

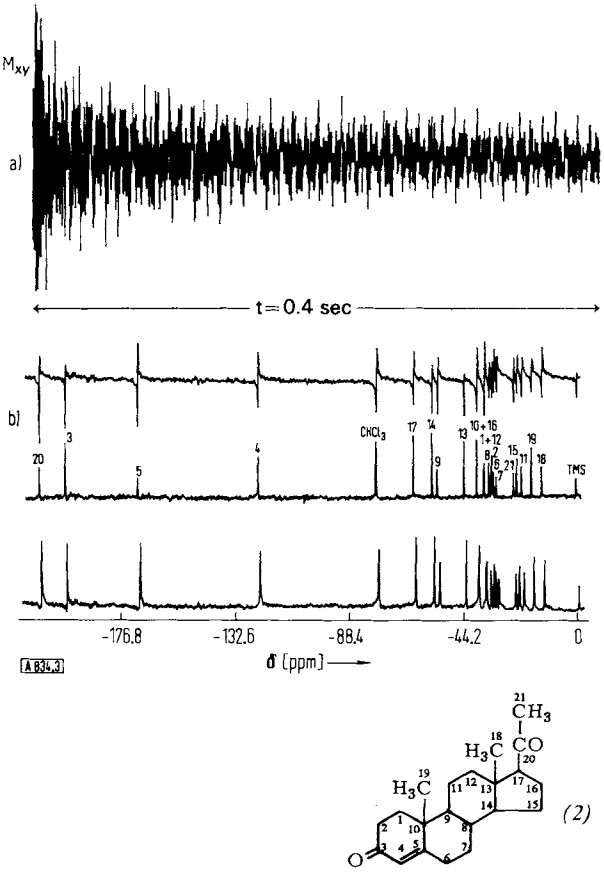
A pulse interferogram is a complex wave function resulting from the superposition of all the Larmor frequencies stimulated by the pulse. Like any complex wave function, therefore, the interferogram can be converted, under certain mathematical conditions, into a spectrum of the Larmor frequencies, *i.e.* into the NMR spectrum itself, by



(1)

Fig. 2. 22.63 MHz PFT ^{13}C-NMR spectrum of quinoline (*1*), transformation of a 15 µs pulse, pulse interval 1.6 s (assignment according to *Pugmire et al.* [7]). The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0.

Fourier transformation[6]. Now a radio-frequency pulse is equivalent to the emission from a multichannel transmitter whose frequency spectrum momentarily stimulates all the Larmor frequencies of a sample simultaneously at



(2)

Fig. 3. a) 22.63 MHz pulse interferogram of progesterone (*2*), ^{1}H broadband decoupled, 1.5 M in chloroform. Accumulation of 1024 pulses, pulse width 30 µs, pulse interval 0.4 s, 4096 data points. b) Fourier transformation of the pulse interferogram of progesterone; from top to bottom: dispersion spectrum; absorption spectrum; magnitude spectrum. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0. Recorded by Bruker Physik AG, Karlsruhe-Forchheim.

full power. However, the sensitivity of an NMR spectrometer increases with the number of channels that stimulate simultaneously[3]. The Fourier transformation of the pulse interferogram, which can be carried out in seconds by a dedicated computer with wired-in multiplication and division, consequently gives an NMR spectrum whose S/N ratio is significantly greater than that of a conventional NMR spectrum of the same sample. A usable NMR spectrum can be recorded within a few seconds in this way. Figure 2 shows the proton-decoupled ^{13}C-NMR spectrum recorded after Fourier transformation of an interferogram obtained from a single pulse lasting 1.6 seconds for pure quinoline *(1)* having the natural ^{13}C abundance of 1.1%. The advantages of the PFT method over conventional NMR spectroscopy are thus a considerable saving of time and the improvement of the S/N ratio by more than one order of magnitude.

The sensitivity can be further increased if the pulse interferograms are accumulated by means of averaging computers before the Fourier transformation. For example, if the time taken to register an interferogram is 0.5 second, which corresponds to the interval between two pulses, 1000 interferograms can be accumulated in the time required to record conventional NMR spectra (500 seconds). According to Section 1, this corresponds to a further increase in the S/N ratio by a factor of $10\sqrt{10}$. As an example, Figure 3 shows the accumulated ^{13}C interferogram of progesterone *(2)* in 1.5 M solution, together with the corresponding Fourier transforms obtained by three different programs.

4.2. The Technique of PFT ^{13}C-NMR Spectroscopy

4.2.1. Shortening of the Pulse Interval with ^{13}C

The similarity of the Fourier transform of an interferogram to a conventionally recorded NMR spectrum of the same sample increases with the time spent in recording the interferogram. In the accumulation of interferograms, therefore, the pulse interval, *i.e.* the time between two pulses, should be as large as possible, and should in no circumstances be appreciably smaller than the longitudinal relaxation time T_1, since the vector $\vec{M}$ (Fig. 1) rotates again in the $\vec{H}_0$ direction T_1 seconds after the application of the pulse.

Since T_1 for ^{13}C is large (up to 1 minute), the accumulation of ^{13}C interferograms would require long pulse intervals and hence long recording times. This difficulty can be overcome by the use of the spin-echo method[8,9]. In this method, a 90° pulse first turns the vector $\vec{M}$ toward the xy plane (cf. Fig. 1b and 1c). The receiver then records an interferogram in the usual manner. Because $T_2 \ll T_1$ in the case of ^{13}C, this interferogram decays more rapidly than $\vec{M}$ turns back into the $\vec{H}_0$ direction. The application of two further pulses of 180 and 90° immediately after the first 90° pulse accelerates the swing back. The 180° pulse forces the vectors of the transversal magnetization $\vec{M}_{xy}$ into the negative xy plane with simultaneous focusing (spin echo), and the subsequent 90° pulse inclines the focused vector back into the $\vec{H}_0$ direction. The pulse sequence 90°—180°—90° can be repeated within fractions of a second (*e.g.* 0.4 second, Fig. 3). As a result, the time required for accumulation of the interferograms is considerably reduced. This method, which can be applied to ^{13}C, is referred to as "driven equilibrium Fourier transform" (DEFT) NMR spectroscopy[8].

4.2.2. Absorption, Dispersion, and Magnitude Spectra

The computer required for the Fourier transformation chops the interferogram into a few thousand data points, depending on its capacity. It takes 10—20 seconds for the scanning of these data points and the Fourier transformation. Depending on the calculation procedure, the transformation gives an absorption spectrum (v mode, Fig. 3b), a dispersion spectrum (u mode, Fig. 3c), or a magnitude spectrum ($(u^2+v^2)^{1/2}$ mode, Fig. 3d).

Figs. 4a—4c illustrate how the magnitude spectrum results from the absorption and dispersion spectrum.

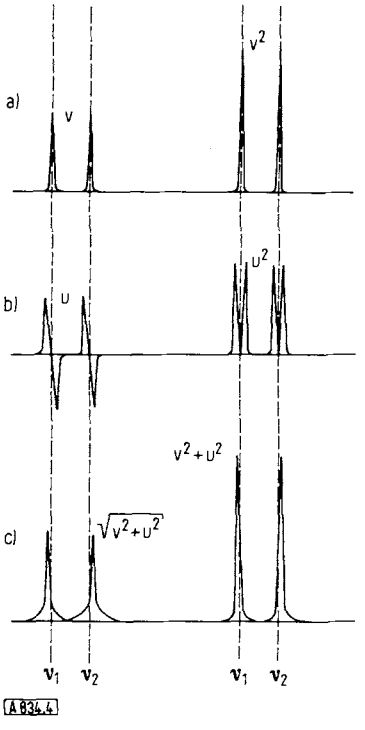


Fig. 4. a) Absorption, b) dispersion, c) magnitude spectrum of two closely spaced signals.

The magnitude spectrum plots the absolute value of the transverse magnetization $\vec{M}_{xy}$ as a function of frequency without reference to the phase. Compared to the absorption spectrum, it has the following advantages:

1. Although exhibiting tailing due to the dispersion part, many signals are more intense (Figs. 3d, 4c).

2. Signals appearing closely together are better separated in the magnitude spectrum due to the dispersion part (Figs. 4a, 4c).

These advantages of magnitude spectra are achieved at the expense of line distortions which are considerable in PFT ^{1}H-NMR spectra. In ^{13}C-NMR magnitude spectra, however, these distortions are mostly within the standard deviation of ^{13}C shifts. Only in the case of weak resonances

near strong signals (*e.g.* solvent peaks) does the frequency distortion of ^{13}C-NMR in the magnitude mode have to be considered[3].

4.2.3. Lock and Standard

A heteronuclear signal, usually the ^{19}F signal of hexafluorobenzene or the ^{2}H signal of deuterium oxide, is used in PFT ^{13}C-NMR spectroscopy to stabilize the field/frequency ratio. Hexafluorobenzene is allowed to rotate with the sample tube in an external centered capillary. Deuterium oxide may be used as the solvent and internal heteronuclear lock substance in the case of water-soluble ^{13}C samples.

The ^{13}C resonance range extends over about 200 ppm. At 22.63 MHz, this is about 4.5 kHz. Carbon disulfide[10] or tetramethylsilane may be used as the standard. The TMS signal is located at a very high field (0 ppm), and the CS_2 signal at a very low field (−192 to −193 ppm relative to TMS, depending upon the solvent, and not −194 ppm as previously reported). Since the region of ^{13}C carbonyl resonance overlaps with the CS_2 signal, whereas only very few signals occur close to and above the TMS signal, TMS has recently gained preference as the standard.

5. Assignment Aids

5.1. ^{1}H Broad-Band Decoupling and Nuclear Overhauser Effect

Since geminal ^{13}C-^{1}H coupling constants are very large (100—250 Hz), the interpretation of ^{13}C-NMR spectra is frequently difficult because of overlapping ^{13}C-^{1}H multiplets. To simplify the spectra and to increase the sensitivity, therefore, the technique of proton broad-band decoupling is often used in PFT ^{13}C-NMR spectroscopy. The ^{13}C sample is continuously irradiated with a second radio frequency $\vec{H}_2$ in addition to the (continuous or) pulse irradiation with the field $\vec{H}_1$. If the frequency band of $\vec{H}_2$ covers the entire range of the Larmor frequencies of the protons, all the ^{13}C-^{1}H multiplets collapse. A singlet therefore appears for each nonequivalent carbon atom. The *S/N* ratio is thus increased by this broad-band decoupling as a result of the collapse of the multiplets, and also by the nuclear Overhauser effect[11].

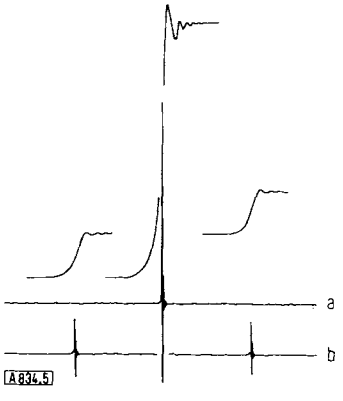


Fig. 5. Nuclear Overhauser effect on ^{1}H broad-band decoupling of ^{13}C-enriched formic acid [12], a) decoupled, b) coupled.

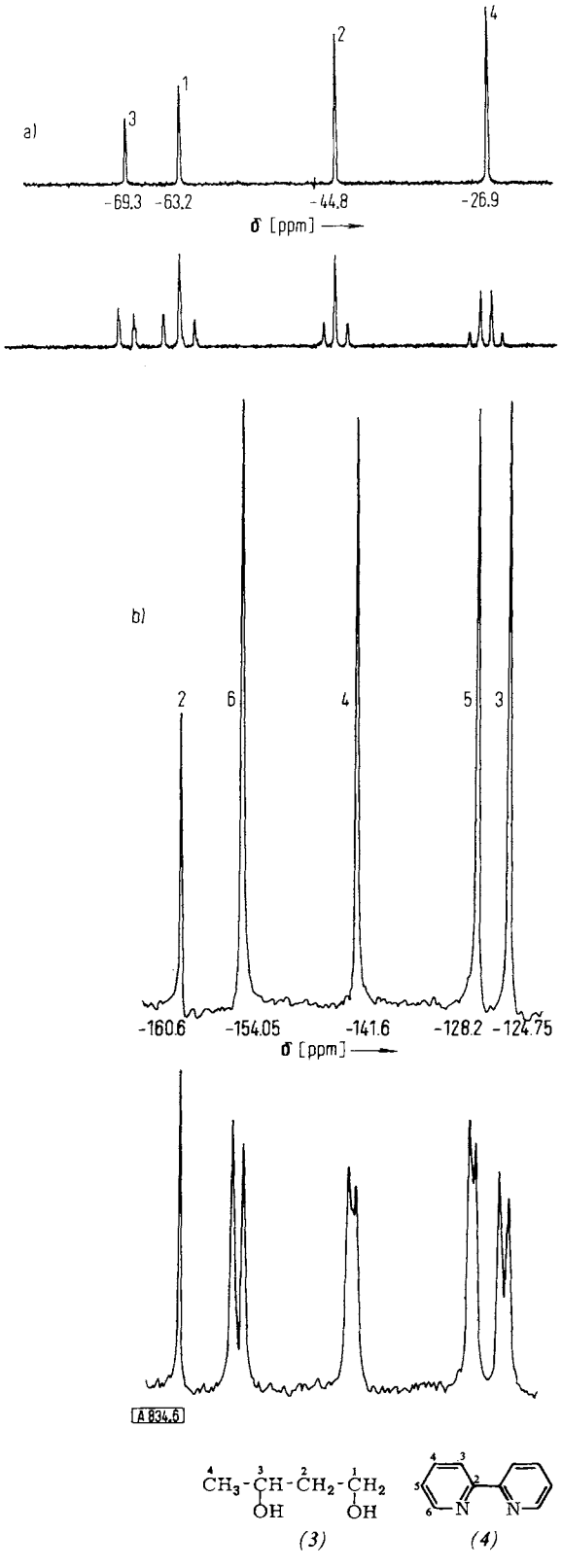


Fig. 6. ^{13}C signal assignment by off-resonance decoupling a) for 1,3-butanediol *(3)*, 22.63 MHz; b) for 2,2'-bipyridine *(4)*, 25.2 MHz. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0. Recorded by a) Bruker Physik AG, Karlsruhe, b) Varian Ass., Palo Alto.

The nuclear Overhauser effect is based on the fact that the natural population of the (^{1}H) spin levels (Fig. 1b) is changed by double resonance stimulation with the field $\vec{H}_2$, the spin state with the higher energy frequently having a higher population than that with the lower energy.

Subsequent relaxation processes (return of the $\vec{M}$ vectors into the $\vec{H}_0$ direction) also influence the occupation of the spin levels of other nuclei by dipole-dipole (transmitter-receiver) interaction. If the spin levels couple, as *e.g.* in the case of geminal and vicinal nuclei, the nuclear Overhauser effect is particularly strong. It leads in the ^{1}H broad-band decoupling of ^{13}C-^{1}H multiplets to a distinct increase in the signal intensities, as is shown by Figure 5 for the ^{13}C resonance of ^{13}C-enriched formic acid[12].

5.2. "Off-Resonance" Decoupling

Though ^{1}H broad-band decoupling simplifies a ^{13}C-NMR spectrum and increases the sensitivity, this technique suppresses valuable clues to the assignment of the signals on the basis of the ^{13}C-^{1}H multiplets.

"Off-resonance" partial decoupling is a valuable aid to the assignment of ^{13}C resonances in such cases. The resulting sensitivity losses as compared with ^{1}H broad-band decoupling are small (Fig. 6).

In this double resonance method[13, 14], the second frequency $\vec{H}_2$ is a few hundred Hz outside the range of the Larmor frequencies of the protons ("off resonance") instead of inside this range. Vicinal and long-range couplings collapse in these circumstances. For this reason, and because of the accompanying nuclear Overhauser effect, the S/N ratio of ^{1}H off-resonance decoupled spectra suffers only a small decrease in comparison with that of ^{1}H broad-band decoupled spectra.

Depending on the frequency range of the $\vec{H}_2$ field, the geminal ^{13}C-^{1}H coupling constants decrease to 10—50 Hz, with the result that a spectrum of intense multiplets of first order is observed (quartets for methyl, triplets for methylene, doublets for methine, and singlets for quarternary C atoms). Figure 6 shows how the assignment of the signals for 1,3-butanediol *(3)* and 2,2'-bipyridine *(4)* follows from the geminal ^{13}C-^{1}H multiplets of the off-resonance ^{13}C spectra.

5.3. Longitudinal Relaxation Times

If relaxation processes are controlled by intramolecular C—H dipole-dipole interactions, the longitudinal relaxation time T_1 of ^{13}C (spin-lattice relaxation time) should depend in a characteristic manner on the number of hydrogen atoms bound directly to carbon[15]. A knowledge of T_1 is therefore a further aid to the assignment of ^{1}H broad-band decoupled ^{13}C resonances. For this reason, the measurement of T_1 in spin echo Fourier transform (SEFT) ^{13}C experiments is becoming increasingly important[3, 16–18].

In SEFT measurements, a 180° pulse first reverses the orientation of all the nuclear spins (Fig. 1). If a 90° pulse follows immediately, the receiver records an FID interferogram as usual. The subsequent Fourier transformation yields an NMR spectrum whose signals are reversed as a result of the 180° pulse. If the interval t between the 90° and the 180° pulses is $t = 1/2\ T_1$, the magnetization in the xy plane becomes 0, and the signal in the spectrum disappears. If t increases further, the signal is reversed again and its intensity rises. The longitudinal relaxation times T_1 of nonequivalent C atoms can therefore be determined by varying the interval t between 90° and 180° pulses and recording the PFT ^{13}C-NMR spectrum for each t (Fig. 7). The pulse sequence and interval, the accumulation of the interferograms, and the Fourier transformation can be controlled by a computer in such a way that the attached pen recorder displaces the spectra as it records them. The

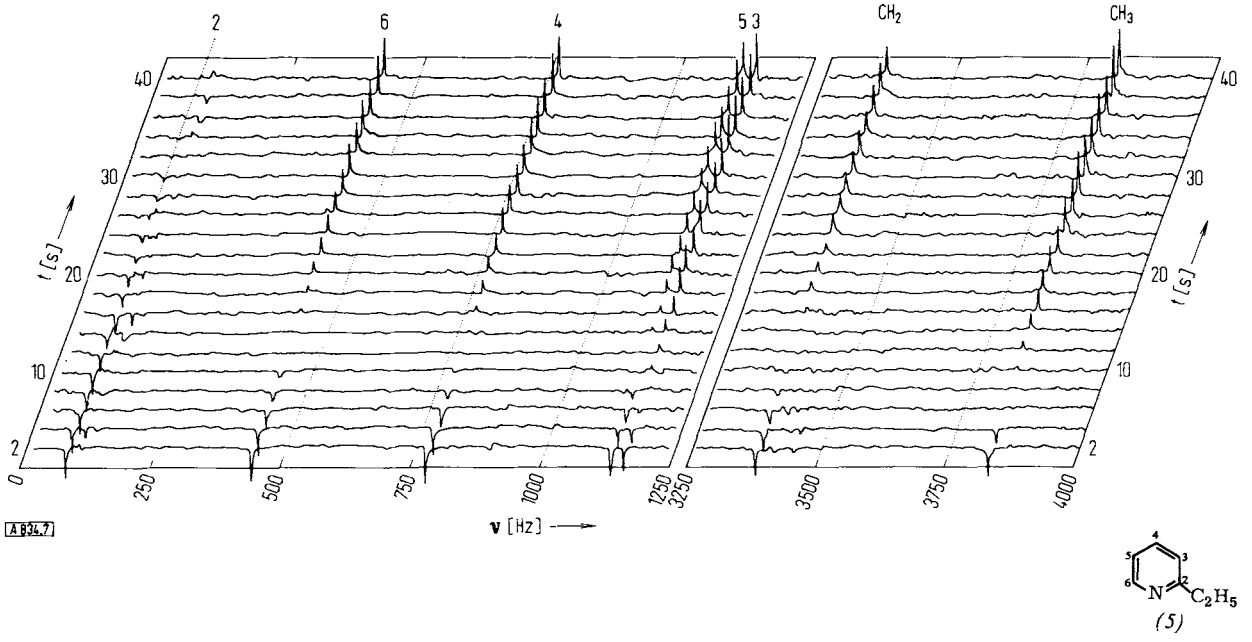


Fig. 7. SEFT measurement of longitudinal relaxation times for 2-ethylpyridine *(5)* [17]. The numbers by the signals indicate the numbering of the C atoms.

result is a three-dimensional representation of the signals as a function of frequency and interval, as shown in Figure 7 for 2-ethylpyridine *(5)*. It can be seen that T_1 increases as the number of directly bonded H atoms decreases:

$$\underset{14.5\,s}{T_1(CH_3)} < \underset{20\,s}{T_1(CH_2)} < \underset{21-23\,s}{T_1(\gtrless C-H)} < \underset{68\,s}{T_1(\gtrless C-)}$$

This sequence confirms that the relaxation process involves mainly protons[15].

Greater longitudinal relaxation times T_1 and the absence of ^{13}C-^{1}H coupling, and hence also of the nuclear Overhauser effect, are therefore the reasons why the ^{13}C signals of quarternary and carbonyl C atoms give the lowest intensities in ^{1}H broad-band decoupled PFT ^{13}C-NMR spectra (see also Fig. 8).

6. PFT ^{13}C-NMR Spectroscopy of Organic Compounds

6.1. ^{13}C Chemical Shifts of Organic Compounds

The ^{13}C resonances of most organic compounds extend from 0 to −200 ppm relative to tetramethylsilane as the standard (Table 1). This is twenty times the ^{1}H resonance range. ^{13}C-NMR spectra therefore show changes in the chemical environment of a C atom not only more directly, but also more distinctly than ^{1}H-NMR spectra. ^{13}C resonances frequently follow patterns similar to those of the ^{1}H shifts.

The ^{13}C shifts of *n*-alkanes are located at very high fields. They obey the Grant-Paul additivity relation[19, 20]:

$$\delta_C(k) = B + \sum_l A_l n_{kl}$$

$\delta_C(k)$ = chemical shift of the k-th C atom
B = chemical shift of methane
A_l = additive parameter of the chemical shift of C atom l
n_{kl} = number of C atoms in position l in relation to C atom k.

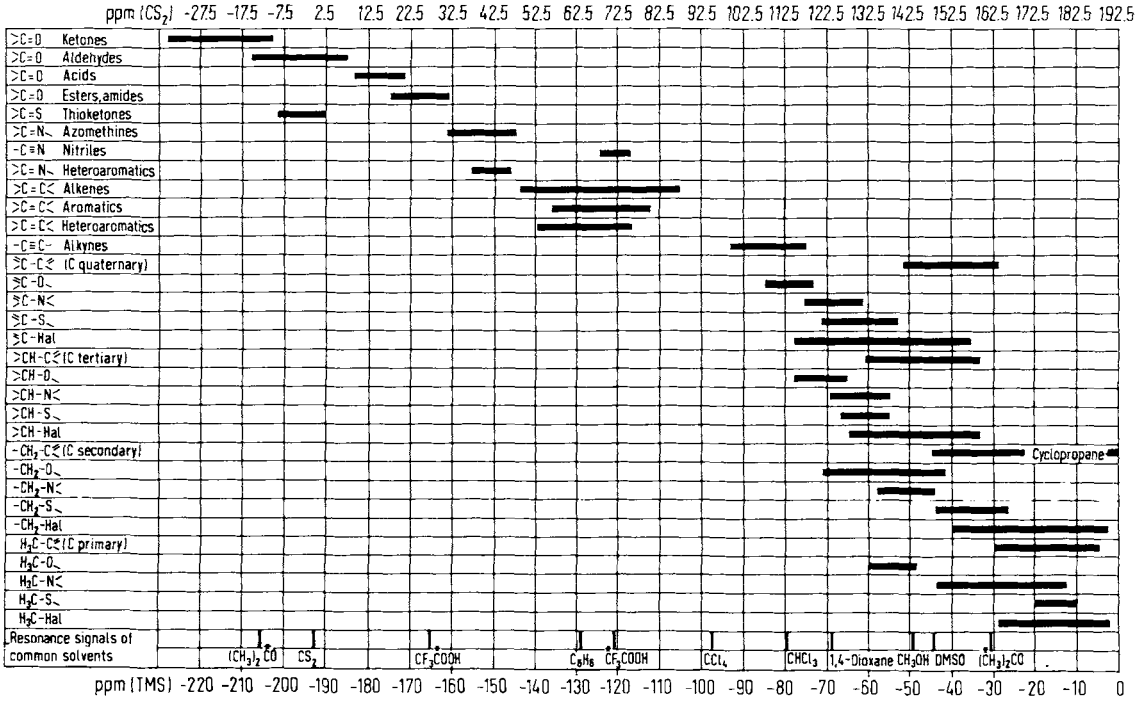
As the number of H atoms bonded geminally to a C atom increases, the corresponding ^{13}C signal moves to higher fields:

$$\delta_{quarternary} > \delta_{tertiary} > \delta_{secondary} > \delta_{primary}$$
(absolute values relative to TMS)

Electron-withdrawing substituents displace the signals of neighboring C atoms to lower fields; the same is true of hetero atoms in heterocycles.

In cycloaliphatic compounds, the ^{13}C resonance of the strained three-membered ring occurs at a surprisingly high field (−2.3 ppm) in relation to the resonances of medium-sized rings (−30 to −24 ppm)[21]. In norcaradienes, however, the ^{13}C signals of the three-membered rings are observed at lower fields than in cyclopropanes themselves[22].

Table 1. ^{13}C-chemical shifts in organic compounds.



The ^{13}C signals of alkynes are higher than those of the alkenes and aromatic compounds, and the shifts of the latter, unlike the ^{1}H resonances, overlap. For cyclically conjugated π systems, *e.g.* in nonbenzoid aromatic

compounds, the ^{13}C signals move linearly toward higher fields with increasing π-electron density per C atom[23].

The only slightly overlapping regions of the carbonyl resonance allow the differentiation of ketones, aldehydes, carboxylic acids, and derivatives of carboxylic acids:

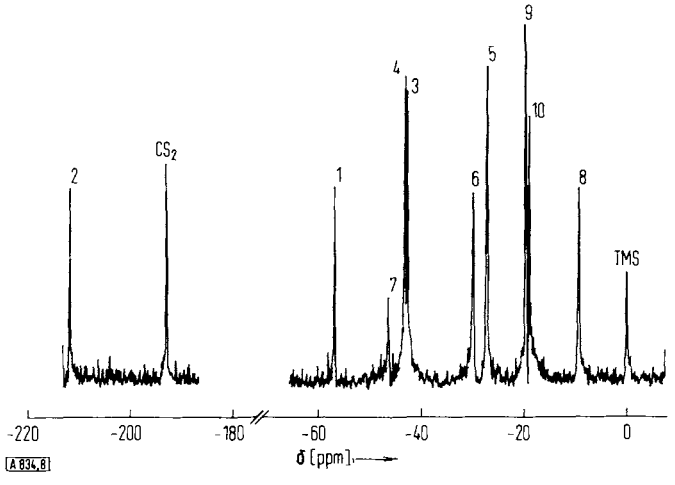
$\delta_{ketone} > \delta_{aldehyde} > \delta_{carboxylic\ acid} > \delta_{ester\ and\ amide}$

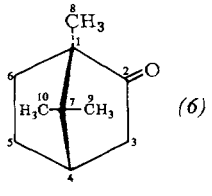
(absolute values relative to TMS)

7. PFT ^{13}C-NMR Spectroscopy of Some Natural Products

7.1. Terpenes and Carotenoids

A number of ^{13}C resonance investigations on carotenoids, terpenes, and particularly norbornyl derivatives have been reported[24-26]. As an example, let us consider the assignment of the signals of the PFT ^{13}C-NMR spectrum of camphor *(6)* (Fig. 8). Methyl carbon (C-8, C-9, C-10), methylene carbon (C-3, C-5, C-6), tertiary carbon (C-4),





(6)

Fig. 8. 22.63 MHz PFT ^{13}C-NMR spectrum of camphor *(6)* in CS_2. 256 pulses, pulse width 40 µs, pulse interval 0.4 s. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0.

and quarternary carbon (C-1, C-7) can be differentiated by off-resonance decoupling. The carbonyl C-atom (C-2) appears at a very low field. The signals of C-2 and C-4 can thus be conclusively assigned. The signal sequence of the methylene C atoms is found from the β-substitution effects of C-2 (C=O) and C-8 (CH_3) to be C-3, C-6, and C-5, in the order of increasing field. The methyl signals (C-9 and C-10) have not yet been definitely assigned[26].

7.2. Steroids

The total assignment of a larger number of ^{13}C steroid spectra has been achieved by off-resonance decoupling, derivatization (*e.g.* acetylation), or specific deuteration and comparison of spectra[27]. However, no Fourier transform ^{13}C-NMR spectra of this class of natural products have previously been described[28]. Figure 3 shows the spectrum recorded by this technique for progesterone. The off-resonance ^{13}C spectrum gives the signal assignment[27] of the CH_3 groups (C-18, C-19, C-21) and quarternary C atoms (C-10, C-13); a quartet is observed for the former and a singlet for the latter. The methylene C atoms of the steroid skeleton, which absorb at very high fields, are C-11 and C-15. Some of the alicyclic ^{13}C atoms are not influenced by electronic effects; of these, the signals of C-9, C-14 and C-17 occur at very low fields. A comparison of the signal positions for several progesterone derivatives gives the assignment of the resonances of C-1, C-6, C-7, C-8, C-12, and C-16. The C-2 signal can be identified by off-resonance decoupling after deuteration of C-2. The resonances of C-4, C-5, C-3, and C-20 are typical for olefinic and carbonyl carbon atoms[29-34].

7.3. Alkaloids

The information obtainable from ^{1}H broad-band decoupled ^{13}C-NMR spectra can be seen particularly clearly in the investigation of alkaloids. The signal assignment of the 20 carbon atoms of the alkaloid gelsemine[37], for example, was achieved purely with the aid of the theory of the chemical shift[19,35,36] and with a minimum of model substances. The presence of polycyclic aliphatic and aromatic rings and of hetero atoms leads to a pronounced differentiation of the ^{13}C signals of alkaloids. The shift differences between the C atoms are therefore large, and this facilitates the assignment on the basis of off-resonance decoupled spectra and the theory of the chemical shift. As was shown in the case of the epimers 10-oxo-de-*N*-morphinan and 10-oxo-de-*N*-isomorphinan, *cis* and *trans* fusion of rings in particular can also be clearly characterized[38].

7.4. Carbohydrates

The first publications on the ^{13}C resonance of carbohydrates[39-42] show that this method admirably complements proton resonance. Only one article describes PFT ^{13}C measurements on glycosides[43].

For the cyclohexane and pyranose rings, the ^{13}C signals of ring C atoms with axial substituents usually appear at higher fields than those of corresponding C atoms with equatorial substituents[36,44,45]. The example of the pair of anomers α- and β-methyl-D-xylopyranoside *(7)* and *(8)* (Fig. 9) shows a number of rules that are found for all pyranosides[43].

The signals of the anomeric carbon atoms C-1 are observed at very low fields. The C-1 signal of methyl-α-D-xylopyranoside, because of the axial methoxy group, is

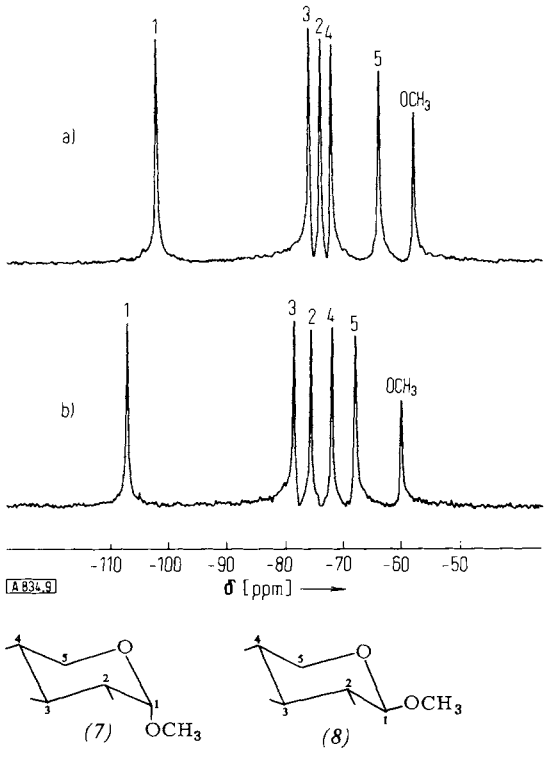
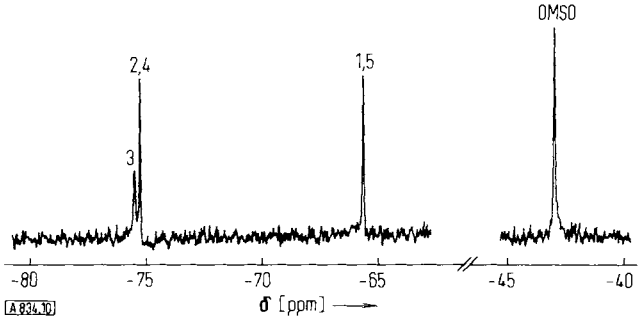
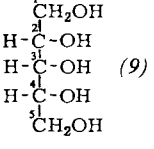


Fig. 9. 22.63 MHz PFT ^{13}C-NMR spectrum of a) α-methyl-D-xylopyranoside *(7)* and b) β-methyl-D-xylopyranoside *(8)*, 2 M in water, 256 pulses, pulse width 30 μs, pulse interval 0.4 s. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0.





(9)

Fig. 10. 22.63 MHz PFT ^{13}C-NMR spectrum of ribitol *(9)* in water: 256 pulses, pulse width 40 μs, pulse interval 0.4 s. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0.

situated at a field 4.5 ppm higher than that of the C-1 signal of the β-anomer, with its equatorial methoxy group. Similarly, the signal of the axial α-methoxy group, which is situated at a very high field, is 1.9 ppm higher than that of the equatorial β-methoxy group. Since no OR group is attached to C-5, this atom has the highest shielding of all the pyranose carbon atoms (Fig. 9). When the configuration of the methoxy group on C-1 changes from equatorial to axial, the signals of C-2, C-3, and C-5 are displaced to higher fields. The signal of C-4, on the other hand, is practically unaffected.

The ^{13}C signals of polyalcohols can be assigned with the aid of the following rules[46]:

1. The ^{13}C signals of the CH_2 or CH_3 groups of deoxypolyols, as expected, are observed at high fields.

2. A hydroxyl group has a strong inductive effect on the C atom attached to it (shift to lower fields)[45].

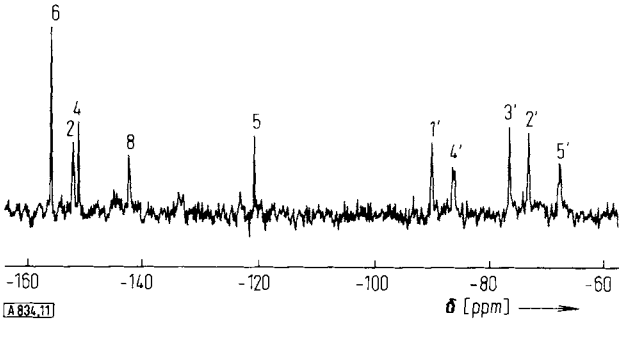
3. For vicinal polyols, the ^{13}C resonances of secondary alcoholic residues are located at lower fields than those of primary alcoholic residues[46].

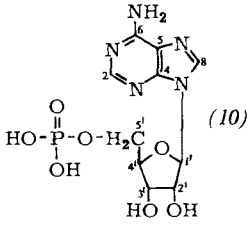
4. Carbon atoms which are equivalent due to configurational symmetry produce identical signals, as can be recognized from their higher intensity[46].

Figure 10 illustrates rules 3 and 4 in the PFT ^{13}C-NMR spectrum of optically inactive ribitol *(9)*. Due to configurational symmetry, C-1 and C-5 give one signal at high field, and C-2 and C-4 give another at lower field. The C-3 signal appears at lowest field, with half the intensity of the other two signals. Pentitols and hexitols of lower symmetry, such as arabitol or sorbitol, give five and six signals respectively[46].

7.5. Nucleosides and Nucleotides

The ^{13}C resonance spectra of purine nucleosides and nucleotides contain two groups of signals, as is shown by the PFT ^{13}C-NMR spectrum of adenosine 5′-monophosphate (muscle adenylic acid) *(10)*. The ribofuranose resonances lie between −64 and −99 ppm, and those of





(10)

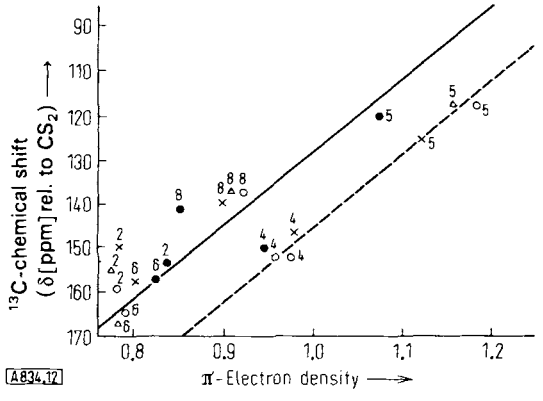
Fig. 11. 22.63 MHz PFT ^{13}C-NMR spectrum of adenosine 5′-monophosphate *(10)* in water: 1024 pulses, pulse width 5 μs, pulse interval 0.4 s. The numbers by the signals indicate the numbering of the C atoms. δ values relative to TMS = 0.

the heterocycle between −95 and −165 ppm (cf. Fig. 11)[47-50]. According to investigations on carbohydrates[39-42] and nucleosides[47-50], the ^{13}C signal of the hydroxymethyl group (C-5′) occurs at a very high field, and that of the anomeric carbon atom (C-1′) at a very low field

within the pentose ^{13}C resonances. Of all the carbohydrate signals, that of C-1′ changes most on variation of the heterocycle. The signal of C-4′ appears as a doublet because of phosphorus-carbon coupling, and is therefore easy to identify. Comparison of ribonucleotides with deoxyribonucleotides allows the assignment of the C-2′ and C-3′ signals.

The signals of C-2 and C-8 of the adenyl residue can be assigned by off-resonance proton decoupling and comparison with the spectra of other purine nucleosides. Further comparisons with the spectra of purine and pyrimidine nucleosides allow the identification of the remaining three quarternary C atoms. In the heterocycle, the C-5 signal appears at the highest field, and the C-6 signal at the lowest field.

It has not yet been possible to detect the helical structure in polynucleotides by ^{13}C resonance using the CAT method. Attempts to determine interactions between various nucleotides from displacements of the ^{13}C resonance have also been unsuccessful so far[47].



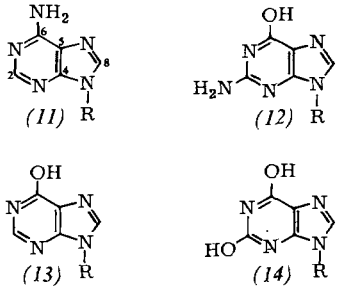


Fig. 12. Relation between ^{13}C chemical shift and π-electron density in the purine nucleosides adenosine *(11)* (●), guanosine *(12)* (△); inosine *(13)* (×), and xanthosine *(14)* (○). The numbers indicate the numbering of the C atoms. R = ribosyl.

Figure 12 shows the relation[48] between the ^{13}C chemical shift and the π-electron density[51] in purine nucleosides. Only the resonances of the ^{13}C—H atoms obey the Spiesecke-Schneider relation[23] (160 ppm/π-electron). The quarternary C atoms obey a different relation (broken line).

7.6. Amino Acids and Oligopeptides

The first ^{13}C resonances of some amino acids were obtained indirectly from INDOR spectra[52] and later from the ^{1}H broad-band decoupled, accumulated 15 MHz ^{13}C-NMR spectra of ^{13}C-enriched (15%) amino acids[53].

The preparation of isotope-enriched amino acids is expensive and time-consuming, and can be considered only for special applications, *e.g.* for the specific incorporation of labeled amino acids into a peptide or for the investigation of enzyme-substrate interactions with ^{13}C-enriched substrates. The advantages of the PFT technique were shown by the ^{13}C spectra of free amino acids, peptides and their derivatives[54–56], and proteins (see Section 7.7) having the natural ^{13}C abundance.

The accumulation of 500 pulses (3.5 minutes) is usually sufficient for recording the spectra of readily soluble amino acids[56]. A satisfactory PFT ^{13}C spectrum (22.63 MHz) of a 0.2 M aqueous solution of the tripeptide glutathione can be obtained in less than 30 min by accumulation of 4000 pulse interferograms with 0.4 s as interval and with ^{1}H decoupling, followed by Fourier transformation[54]. To obtain easily assignable spectra of peptide antibiotics such as gramicidin and smaller peptide hormones such as oxytocin and vasopressin, recording times of about 3 hours are required with 0.05–0.1 M solutions[57].

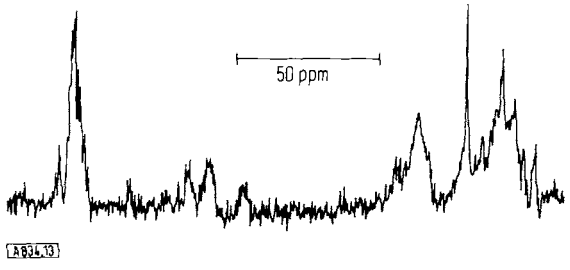


Fig. 13. 22.63 MHz ^{13}C-NMR spectrum of carboxymyoglobin, 8×10^{-3} M in 0.1 M phosphate buffer, 240000 pulses, pulse width 60 μs, pulse interval 0.4 s, 2048 data points. Recorded by Bruker Physik AG, Karlsruhe-Forchheim.

^{13}C-NMR shifts of amino acids and peptides cover a range from about −15 to −180 ppm relative to TMS (see Fig. 13). The ^{13}C resonances of the carbonyl groups (carboxyl, carboxamide, hydrazide, ester and oxycarbonyl groups of protected derivatives, and peptide linkages) appear at the lowest fields (−160 to −180 ppm). The signals of aromatic and heteroaromatic substituents on C-α (phenyl, indolyl, imidazolyl) appear between −120 and −145 ppm. The ^{13}C-α signals are observed between −50 and −65 ppm, and characterize each amino acid. The resonances of C-β and C-γ aliphatic side chains occur at higher fields (−15 to −40 ppm) (for review see[56]). The assignment of signals for the individual amino acids is most readily achieved by comparison of spectra of homologous series or by comparison with the values estimated from the additivity rules given by *Grant et al.*[19, 58], which agree well with the observed ppm values[52]. In cases of doubt, the resonances can be definitely assigned on the basis of off-resonance ^{1}H decoupled spectra or by a change of solvent or of the pH value. The signals of the side chains of amino acids, even in protected derivatives and peptides, appear to depend only slightly on the solvent (2–3 ppm); however, only a few comparative measurements in water, DMSO[56], and methanol[59] have so far been carried out.

The measurement of the pH dependence of the ^{13}C spectra of some simple amino acids and peptides give pK values

for the NH_3^+ and COOH groups that exhibited excellent agreement with those obtained by other methods[52]. With increasing pH value (dissociation of the protons from COOH and NH_3^+), the ^{13}C resonances are slightly displaced to lower fields (2–4 ppm) because of the change in charge density on C-α. According to *Del Re et al.*[60], the charge density distribution can be determined semi-empirically for amino acids[52]. The anomalous shift to lower fields (shift to higher fields) of the ^{13}C signals on deprotonation (protonation) is also observed for amines, carboxylic acids, and phosphoric acid systems. This behavior contrasts with the shift of the ^1H signals to higher fields with rising pH value. This cannot be attributed to inductive effects or to a change in hybridization, since no change in the coupling constants is observed. The opposite shifts of the ^{13}C and ^1H signals can be interpreted to a first approximation as a result of polarization of the C—H bonds by the ammonium or carboxylate group, with the result that the electron density on the carbon decreases, while that on the hydrogen increases[52].

The measurement of the pH dependence of the ^{13}C spectra of polyfunctional amino acids and peptides by the PFT technique allows a new determination of the p*K* and pI values of these compounds[57]. Since the ^{13}C-α signals of cysteine and cystine differ by 13 ppm[54], it is possible to investigate the pH dependence of the redox equilibria of these amino acids and of peptides such as glutathione, whereas this is extremely difficult *e.g.* by polarographic and other methods[61].

7.7. Polypeptides and Proteins

The interpretation of the ^1H-NMR spectra of polypeptides and proteins presents considerable difficulties, despite the development of high-resolution, superconducting magnetcoils and of the CAT technique[62–68]. More information can be obtained from ^1H-NMR spectra by the use of partly deuterated enzymes[69] or by the use of selective contact shift reagents[70], but this often results in a partial loss of resolution.

On the other hand, the singlets of all the carbon atoms can be detected and assigned in the ^1H noise-decoupled PFT ^{13}C spectra, even in the case of decapeptides. Since the line width of the ^{13}C signals is about 1/16 less than that of the ^1H-NMR signals of macromolecules[59], while the chemical shifts are greater, the probability of overlapping of several signals is extremely small except in the carbonyl region. Preliminary investigations of the sequence dependence of the ^{13}C signals show that a definite sequence analysis is possible only up to tripeptides and tetrapeptides[52, 56].

The ^{13}C spectra of the decapeptide antibiotic gramicidin S-A[59] and of the carbohydrate hydrolase lysozyme (molecular weight 14300; 129 amino acids; accumulation for 87 hours)[71] have been recorded by simple accumulation with broad-band ^1H decoupling. Much more informative ^{13}C spectra of larger peptide hormones such as insulin[72], of enzymes such as ribonuclease[73], and of proteins (carboxymyoglobin, Fig. 13) can be obtained in shorter accumulation times (10–20 hours with 0.02 M solutions) by the PTF-NMR technique. Longer accumulation times are limited less by the long-term stability of the magnet than by the capacity of the computer, and do not allow appreciable improvement in the case of the ^{13}C-NMR spectra of complex biopolymers.

The PFT ^{13}C-NMR spectrum of carboxymyoglobin (153 amino acids, Fig. 13) shows the typical absorption region of the peptide and side-chain carbonyl groups at the lowest fields. This region is followed by the resonances of the side chains of aromatic amino acids, particularly the signals of the twelve histidines and six phenylalanines. The C-α signals, then the C-β, C-γ, and methyl resonances of the side chains of aliphatic amino acids appear at higher fields. The signal intensity in the region of the absorption of the guanidinium carbon atoms (at −155 ppm) is naturally lower for myoglobin (4 arginines) than *e.g.* for lysozyme[71] (11 arginines). This interpretation of such ^{13}C spectra of biopolymers is simplified by comparison with a computer-simulated spectrum, as has already been shown for lysozyme[71]. A comparison of the estimated signal intensities of the various resonance regions with the integrated PFT ^{13}C-NMR spectrum of ribonuclease shows that these agree well with the experimental values[73].

The different ^1H resonances of left-handed and right-handed helices are attributed to the magnetic anisotropy of the carbonyl groups. Field effects should have a greater influence on the ^{13}C shifts in ^{13}C-NMR spectroscopy, and should predominate over the magnetic anisotropy effect of the carbonyl group. Thus larger ^{13}C signal shifts should be found between random coil conformations of polypeptides and left-handed or right-handed helices. Direct steric interactions in proteins with special conformations should also result in pronounced sterically induced shifts[52].

The few reported ^{13}C-NMR studies in the peptide field already give evidence that PFT ^{13}C-NMR spectroscopy will provide the answer to many important biochemical questions regarding the carbon skeleton of these biopolymers.

8. ^{13}C-NMR Contact Shifts and Asymmetry Effects

In addition to the recent uses of contact shift reagents in ^1H-NMR spectroscopy, the contact shift of ^1H-decoupled ^{13}C-NMR signals in the presence of paramagnetic metal complexes is also already being investigated[74–77].

Studies on ^{13}C contact shifts for π-electron systems[74, 76, 77] and σ-electron systems[75] show that the ^{13}C resonances, like the ^1H resonances, depend on the concentration of the added shift reagent. The ^{13}C shifts (up to 6 ppm) in nickel pentanedionate complexes of piperidine and *N*-alkylpiperidines have been used for the investigation of the configuration and the nature of the electron spin density distribution through the σ-electron system[75]. The contact interaction also influences the ^{13}C relaxation. Therefore paramagnetic metal ions are used to prevent changes of ^{13}C signal intensities due to nuclear Overhauser effects during ^1H broad-band decoupling[11].

Molecular asymmetry effects on ^{13}C-NMR shifts have been observed for isopropylalkyl alcohols and isopropylalkanes[78]. The nonequivalence ($\delta_A - \delta_B$) of the methyl groups A and B of the isopropyl group due to the proximity of a center of asymmetry increases from 0.1 to 7.2 ppm in the order alkyl = methyl, ethyl, isopropyl, *tert*-butyl. This is explained by the increase in population of a preferred conformation with CH_{3A} ($\delta_A > \delta_B$ rel. to CS_2) between hydrogen and the hydroxyl group on a hydroxymethyl group[78]. This asymmetry shift is much greater for ^{13}C than for ^{1}H. The nonequivalence of the methyl groups in the isopropyl residue in the vicinity of an asymmetric C atom can be observed particularly clearly in the PFT ^{13}C-NMR spectra of valine, leucine, and their derivatives[56]. PFT ^{13}C-NMR spectroscopy can replace ^{1}H-NMR spectroscopy in particular in the structural elucidation and determination of the enantiomeric purity of diastereoisomers.

9. Isotope Effects and Elucidation of Biosynthetic Pathways

In the elucidation of structures and reaction courses, isotopes such as ^{2}H or ^{13}C are frequently introduced into certain positions in a molecule. PFT ^{13}C-NMR spectroscopy can be used to follow such experiments analytically. The isotope shift of ^{13}C signals is very large; thus the ^{13}C triplet of hexadeuteriobenzene is 13 ppm higher than the benzene singlet in the ^{1}H-decoupled ^{13}C-NMR spectrum. Moreover, the positions of deuterium in deuterated compounds can be determined by comparison of the ^{1}H-decoupled PFT ^{13}C-NMR spectra with the simultaneously ^{1}H- and ^{2}H-decoupled spectra. This is illustrated in Figure 14 for *cis*-3,3,4,7,8,8-hexadeuteriotricyclo[5.1.0.0^{2,4}]octane *(15)*[79]. If the ^{13}C-NMR spectrum is only ^{1}H-decoupled, the C atoms bound to ^{2}H appear as weak multiplets because of the absence of the Overhauser effect.

It is also possible with the aid of PFT ^{13}C-NMR spectroscopy to follow each C atom of a natural product during its biosynthesis. By the use of ^{13}C-enriched starting materials ($^{13}CO_2$, ^{13}C-acetate) or ^{13}C-labeled metabolites in the culture media, it is possible to obtain specifically labeled metabolites or end products, which can be analyzed by ^{13}C-NMR spectroscopy. The ^{13}C-labeled positions are recognized by the high intensity of the corresponding signals. In a double experiment, the aflatoxin precursor sterigmatocystine was isolated from cultures of *Aspergillus versicolor* that had been grown in one case with sodium [1-^{13}C]-acetate and in the other with sodium [2-^{13}C]-acetate as a carbon source. It was possible to establish conclusively the source of each carbon atom in sterigmatocystine by interpretation of the ^{1}H-decoupled accumulated 25.15 MHz ^{13}C-NMR spectra of the two labeled metabolites. This work verified a recently published hypothesis on the biogenesis of sterigmatocystine[80].

Though considerable quantities of substance are still required for biosynthetic studies by PFT ^{13}C-NMR measurements, the radioisotope methods that have been usual until now can in many cases be replaced by this new NMR technique.

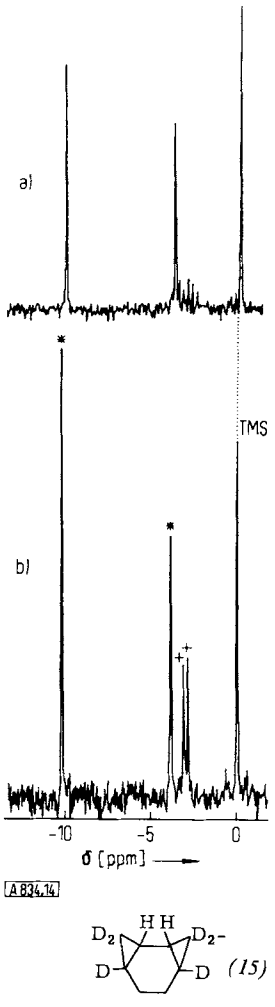


Fig. 14. 22.63 MHz PFT ^{13}C-NMR spectrum of *cis*-3,3,4,7,8,8-hexadeuteriotricyclo[5.1.0.0^{2,4}]octane *(15)*, 20% in hexafluorobenzene/TMS, 4000 pulses, pulse width 40 μs, pulse interval 0.4 s. a) ^{1}H broad-band decoupled, b) ^{1}H and ^{2}H broad-band decoupled, C-^{1}H (*), C-^{2}H (+). δ values relative to TMS = 0.

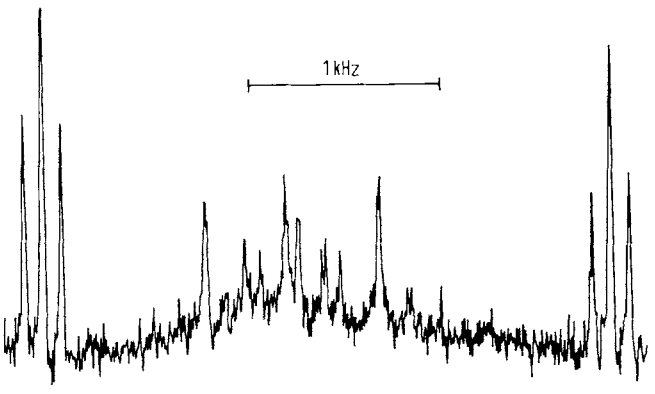
10. PFT ^{13}C-NMR Measurements in Nonliquid Phases

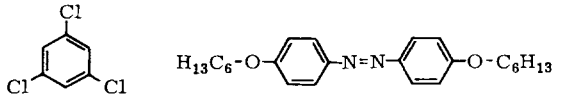
10.1. Nematic Phases

In the liquid phase, the NMR spectrum of a dissolved compound is isotropic, *i.e.* equivalent nuclei produce a single signal. Nematic phases (liquid crystals) restrict the movement of dissolved molecules. In a magnetic field, the dissolved molecules orient themselves in certain directions, which depend on the molecular geometry. The NMR spectrum consequently becomes anisotropic, *i.e.* equivalent nuclei give multiplets as a result of such orientations.

The ^{1}H-NMR spectrum of 1,3,5-trichlorobenzene consists of a singlet in the liquid phase, and of a triplet in the nematic phase (4,4'-di-*n*-hexyloxyazobenzene *(17)* at 80 °C)[81,82].

Because of the low sensitivity of the ^{13}C resonance, it was formerly difficult to record ^{13}C-NMR spectra in nematic phases, since the aggregates of liquid crystals collapse even at medium concentrations of dissolved compounds (approximately 20%)[82]. Figure 15 shows for the case of 1,3,5-

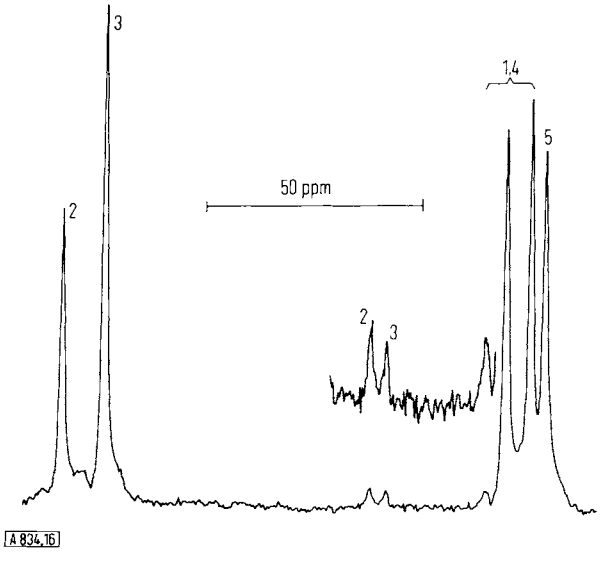


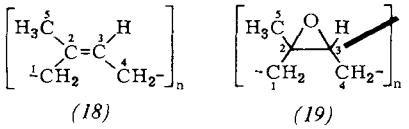


(16) (17)

Fig. 15. PFT ^{13}C-NMR spectrum of 1,3,5-trichlorobenzene *(16)*, 13% in nematic phase 4 (Merck) at 297°K; 85000 pulses, pulse width 40 µs, pulse interval 0.4 s.

trichlorobenzene that the PFT technique enables one to record ^{13}C spectra in nematic phases[79]. The two triplets, which are separated by about 3 kHz, correspond to the C—H atoms. Between these, the C—Cl signals overlap with the broad signal of the nematic phase. The spectrum is being analyzed at present[79].





(18) (19)

Fig. 16. ^{1}H broad-band decoupled 22.63 MHz PFT ^{13}C-NMR spectrum of natural rubber containing 5% of isoprene oxide, 100%, solid, ext. D_2O as lock substance, 8000 pulses, pulse width 40 µs, pulse interval 0.2 s. The assignment of the isoprene units *(18)* is shown in the overall spectrum, and that of the isoprene oxide units *(19)* in the enlarged partial spectrum.

High-resolution NMR studies on polymers have been hindered until now by solubility. Because of the small line width of ^{13}C signals[59], ^{13}C measurements are possible even in highly viscous and solid phases. This has been demonstrated by the recording of PFT ^{13}C-NMR spectra of many polymers in the solid phase[79].

As an example, Figure 16 shows the ^{1}H broad-band decoupled PFT ^{13}C-NMR spectrum of natural rubber containing 5% of isoprene oxide. All the types of C atoms present in this macromolecule can be readily recognized.

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Non-rigid Molecular Skeletons—Berry Pseudorotation and Turnstile Rotation[**]

By Paul Gillespie, Peter Hoffman, Hans Klusacek, Dieter Marquarding, S. Pfohl, Fausto Ramirez, E. A. Tsolis, and Ivar Ugi[*]

Molecules rearrange by regular and irregular processes. The former occur with preservation of bonds and coordination numbers while the latter involve rupture and reformation of bonds via states possessing different coordination numbers. For molecules with skeletons that carry n ligands both processes can be represented by permutation operators belonging to the symmetrical group S_n. These operators are obtained from the descriptors of the particular molecules in a simple manner; the conceivable reaction mechanisms correspond to the skeletal symmetry subclasses of S_n. Regular rearrangements—e.g. of phosphorane derivatives with a monocentric skeleton, including their analogs, or of ethane derivatives with a dicentric skeleton—all submit themselves to classification based upon skeletal non-rigidity. Flexible molecular skeletons are representable by a collection of rigid skeletal models which can be interconverted by deformations of bond angles and/or some form of internal rotation. To accomplish mechanistic understanding of these regular processes, it is useful to represent the symmetries of the rigid skeletal models and the existent ligand equivalencies by subgroups of S_n and consider the dependence of the skeletal flexibility upon the given ligand set. This procedure is based on the ideas of Polya and Longuet-Higgins. The former introduced separation of permutational molecular symmetry into skeletal symmetry and ligand set symmetry, which, combined with the total molecular symmetry concept developed by Longuet-Higgins for the treatment of non-rigid symmetric molecules, yield the foundation for the following classification of regular pentacoordinate rearrangements and related processes. It will be shown that with the given quantum chemical properties of the pentacoordinate phosphorus bond system, including participation of the P_{3d} orbital set, not only the BPR[2] mechanism but also single and multiple TR[2] processes must be considered in the interpretation of the observed phenomena. Although some experimental observations can be interpreted by either of the two mechanisms, and certain other regular rearrangements can be explained only by invoking the TR mechanism, no regular processes are known, as yet, that can be explained solely by the BPR mechanism.

1. Introduction

In recent years, chemical compounds with non-rigid molecular skeletons have attracted wide interest. Rearrangements of monocentric molecules that correspond to permutations of ligands or skeletal positions by bond angle deformations at the central atom[5–7], as well as the conformational interconversions of polycentric systems[8–10] by rotation about bond axes, have been the subject of much discussion.

In this paper, we generate a general approach to the description of the static and the dynamic properties of molecules with flexible skeletons, particular attention being paid to pentacoordinate phosphorus compounds and the properties of their bond systems. Further pursuit of *Polya*'s dual symmetry approach[10] that has been extended by *DeBrujin*[10] and *Ruch et al.*[11], in concert with the total molecular symmetry of *Longuet-Higgins*, will yield a formalism that simultaneously contains the symmetry of the rigid molecular models and their regular rearrangements. In this context the descriptors of permutational isomers, as derived previously[1], become very useful.

2. The Classification of Pentacoordinate Molecules

2.1. Symmetry Equivalencies

Chemical compounds can be arranged into classes of isomers, *i.e.* into classes of compounds with the same molecular formula. Within a class of isomers it is possible, in certain cases, to further classify according to the properties of the permutation groups representing the skeleton and ligand set. *Permutational isomers* differ only by the distribution of the ligand set on the molecular skeleton[1]; those with the same chemical constitution are stereoisomers[12].

The concept of permutational isomerism not only provides a basis for the nomenclatural classification of molecules but also for the characterization and interpretation of their

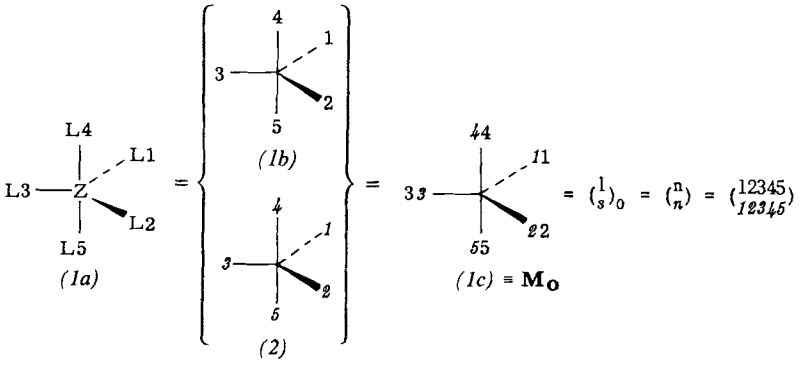
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[**] Chemistry and Logical Structures, Part 2.—Part 1: [1].

intramolecular rearrangements. This is accomplished by mapping the species under consideration onto algebraic structures[11].

Rearrangement processes of molecules with the general formula *(1a)* are the predominant subject of this paper. Molecules of this type are conceptually viewed as a set of ligands and a pentacoordinate central atom Z whose valencies form a TBP[12] molecular skeleton *(2)* with D_{3h} symmetry.

Skeleton *(2)* can also be represented by the set of numbers, $\mathfrak{S}=\{1,\ldots,5\}$, by assigning skeletal numbers to *(2)*. If we now describe the set of ligands $L=\{L_1,\ldots,L_5\}$ by the set of ligand indices $\mathfrak{L}=\{1,\ldots,5\}$ we are now able to represent



the molecule *(1a)* by the formulas *(1b)+(2)* or *(1c)* respectively. This representation is equivalent to the $2\times n$ mapping matrix $\begin{pmatrix}1\\s\end{pmatrix}_0$. Thus formula *(1b)* is merely an abbreviated notation for *(1a)*, whereas *(1c)*, as well as the matrix $\begin{pmatrix}1\\s\end{pmatrix}_0$, not only corresponds to *(1a)* but contains the statement that with skeletal numbering according to *(2)*, the ligand L_1 occupies the skeletal position *1*, ligand L_2 occupies skeletal position *2*, *etc.* If we now define the rule by which the ligands are to be indexed by employing the *Sequence Rule* of *Cahn, Ingold,* and *Prelog*[13], then *(1c)* or $\begin{pmatrix}1\\s\end{pmatrix}_0$ corresponds to that isomer which we call the reference isomer $\mathbf{M}_0$. The reference matrix $\begin{pmatrix}1\\s\end{pmatrix}_0$ is generated when the ligand index set $\mathfrak{L}$ is mapped onto the skeletal index set $\mathfrak{S}$ such that equal numbers are "paired".

From the reference isomer $(1)\equiv\mathbf{M}_0$ we obtain its permutation isomers $\mathbf{M}_\sigma$ by applying the permutations $\boldsymbol{P}_\sigma$ to the ligands $L_1,\ldots,L_5$ (*e.g.* $(1)\rightarrow(3)$), or the permutations $\boldsymbol{Q}_\sigma$ to the skeletal positions according to eq. (1).

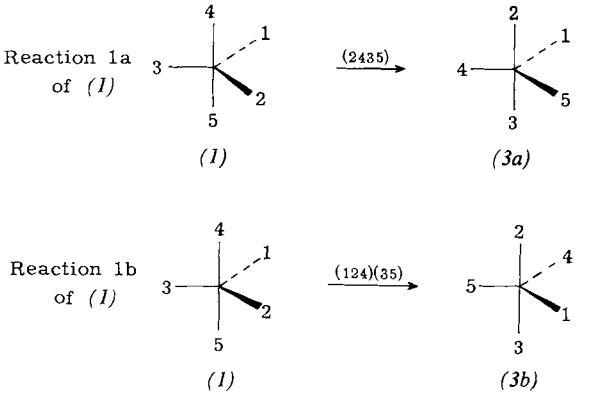
$$\begin{pmatrix}1\\s\end{pmatrix}_\sigma = \boldsymbol{P}_\sigma\begin{pmatrix}1\\s\end{pmatrix}_0 = \begin{pmatrix}\boldsymbol{P}_\sigma 1\\n\end{pmatrix} = \boldsymbol{Q}_\sigma\begin{pmatrix}1\\s_0\end{pmatrix} = \begin{pmatrix}n\\\boldsymbol{Q}_\sigma n\end{pmatrix} \qquad (1)$$

Two such mappings, $\begin{pmatrix}1\\s\end{pmatrix}_\sigma$ and $\begin{pmatrix}1\\s\end{pmatrix}_{\sigma'}$, representing the permutational isomers $\mathbf{M}_\sigma$ and $\mathbf{M}_{\sigma'}$, belong to the same molecule, *i.e.* $\begin{pmatrix}1\\s\end{pmatrix}_\sigma = \begin{pmatrix}1\\s\end{pmatrix}_{\sigma'}$ and $\mathbf{M}_\sigma=\mathbf{M}_{\sigma'}$, if they differ only by the simultaneous permutation $\boldsymbol{R}$ of the ligand indices 1 and the skeletal indices *s* according to eq. (2). With no skeletal symmetry, a pentacoordinate molecule with five different ligands could yield 5! distinguishable isomers corresponding to the 5! different mappings of the set $\mathfrak{L}$ onto the set $\mathfrak{S}$ represented by their $\begin{pmatrix}1\\s\end{pmatrix}_\sigma$ matrices.

$$\begin{pmatrix}1\\s\end{pmatrix}_\sigma = \boldsymbol{R}\begin{pmatrix}1\\s\end{pmatrix}_{\sigma'} \quad \text{or} \quad \begin{pmatrix}\boldsymbol{P}_\sigma n\\n\end{pmatrix} = \begin{pmatrix}\boldsymbol{R}\,\boldsymbol{P}_\sigma n\\\boldsymbol{R}\,n\end{pmatrix} \qquad (2)$$

If however some elements of skeletal symmetry exist, as in *(2)* for example, then the number of distinguishable isomers is reduced. Owing to the D_{3h} symmetry of *(2)*, certain permutational isomers resulting from skeletal or ligand permutations on *(1)* can be interconverted by rotations belonging to the D_{3h} symmetry group and therefore are equivalent.

The C_2 rotations (twofold: $\triangleq 180°$) of the skeleton *(2)* correspond to the permutations *(1 2) (4 5)*, *(1 3) (4 5)* and *(2 3) (4 5)*, and the C_3 rotations (threefold: $\triangleq 120°$) of *(2)* are represented by the permutations *(1 2 3)* and *(1 3 2)* of the skeletal positions. Here, *(1 2 3)* means position *1* replaces position *2*, position *2* replaces position *3* and position *3* replaces *1*, *i.e.* $1\overset{\nearrow 2}{\underset{\nwarrow 3}{\downarrow}}$. These and the identity operation *E* ("do nothing") form a permutation group. The *rigid skeletal equivalence group* $\boldsymbol{G}$ of order $g=6$, represents the rotational symmetries of the rigid skeletal model *(2)* (see Section 4.2.1). Molecules whose $\begin{pmatrix}1\\s\end{pmatrix}$ mappings are numerically transformed into each other by permutations belonging to $\boldsymbol{G}$ are equivalent. With five different ligands on the skeleton *(2)* there are $5!/6=20$ distinguishable permutational isomers corresponding to 10 pairs of antipodes.



Certain ligand permutations, resulting from isomerization processes (see Section 5), are equivalent to certain other permutations due to their skeletal symmetry. For instance, the permutation (2 4 3 5) transforms *(1)* into *(3)* according to *(1)* → *(3a)*. The same isomer results from *(1)* by applying the permutation (1 2 4)(3 5) as well, shown as *(1)* → *(3b)*.

Molecules *(3a)* and *(3b)* are equivalent as they are interconverted by a 120° rotation about the skeletal C_3 axis.

In the $\binom{l}{s}$ matrix representation the equivalence of the permutations (2 4 3 5) and (1 2 4)(3 5) upon *(1)* as well as the permutations (1 2 5)(3 4), (1 3 4)(2 5) and (1 3 5)(2 4) follows from:

$$\binom{l}{s}_{(3a)} = \binom{(2\,4\,3\,5)\,n}{\quad n} = \binom{(2\,4\,3\,5)\,1\,2\,3\,4\,5}{\quad 1\,2\,3\,4\,5} = \binom{1\,5\,4\,2\,3}{1\,2\,3\,4\,5}$$

with $R = (2\,4\,3\,5)^{-1}$, $\binom{R}{R}\binom{1\,5\,4\,2\,3}{1\,2\,3\,4\,5} = \binom{1\,2\,3\,4\,5}{1\,4\,5\,3\,2}$

$$\binom{l}{s}_{(3b)} = \binom{(1\,2\,4)(3\,5)\,n}{\quad n} = \binom{(1\,2\,4)(3\,5)\,1\,2\,3\,4\,5}{\quad 1\,2\,3\,4\,5} = \binom{4\,1\,5\,2\,3}{1\,2\,3\,4\,5} = \binom{1\,2\,3\,4\,5}{2\,4\,5\,1\,3} \quad \text{with } R = (3\,5)(1\,2\,4)^{-1} \tag{4}$$

The resulting matrices of eq. (3) and (4) represent the same molecule as they differ only by the skeletal permutation (*1 3 2*) representing a C_3 rotation of the skeleton given by eq. (5).

$$\binom{\quad 1\,2\,3\,4\,5}{(1\,3\,2)\,1\,4\,5\,3\,2} = \binom{1\,2\,3\,4\,5}{2\,4\,5\,1\,3} \tag{5}$$

If the ligand set $L=\{L_1,\ldots,L_5\}$ contains sets of equivalent ligands rather than five different ones, these equivalencies must be accounted for by permutations representing the permutational symmetry of the ligand set. When two of the ligands of *(1)* are not distinguishable, there are 10 isomers (rather than 20), with 3 pairs of antipodes.

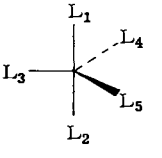
In 1937, *Polya*[10] recognized that classification and enumeration of the isomers of a skeletal class with n skeletal positions is possible only if the permutations of the skeletal equivalence group $\boldsymbol{G}$ and the permutations of the ligand equivalence group $\boldsymbol{H} \subset \boldsymbol{S}_n$ of the order h are taken into account simultaneously. This he accomplished by considering all arrangements as equivalent which differ only by permutations belonging to $\boldsymbol{H}$ and/or $\boldsymbol{G}$ (see Section 3.4). *Polya* called the distinguishable isomers the ***HG configurations*** and gave a combinatorial procedure to enumerate them, illustrating this concept with a hexacoordinate molecule. Six different ligands on an asymmetric skeleton leads to $6!=720$ isomers, whereas the same ligand set on a skeleton with octahedral O_h symmetry, where $g=24$, yields $6!/24=30$ isomers. A ligand set with subsets of two and three equivalent ligands possesses a ligand equivalence group $\boldsymbol{H}$ of order $h=2!\times 3!=12$ on an asymmetric skeleton where $n=6$ corresponds to $6!/12=60$ isomers. The same ligand set on an octahedral skeleton gives just three distinguishable isomers.

Ruch et al.[11] developed *Polya*'s concept further by noting that the set of isomers in a skeletal class or $\boldsymbol{HG}$ configurations respectively corresponds to a system of representatives of the double cosets of the subgroup $\boldsymbol{H}$ and $\boldsymbol{G}$ of the group $\boldsymbol{S}_n$. Further these authors indicate an elegant group theoretical procedure for enumerating these double cosets.

2.2. Nomenclature

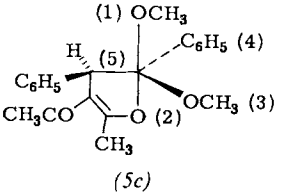
We found that the permutational representation of the mappings of ligand indices, partially symmetrized relative to $\boldsymbol{H}$, onto the set of skeletal indices, partially symmetrized relative to $\boldsymbol{G}$, yields a universally applicable classification for permutational isomers which can serve as a nomenclature system as well[1]. A singular advantage of the use of permutation operators (descriptors) in a nomenclature system is that they provide a basis for the algebraic treatment of permutational isomerization processes and their mechanisms (see Section 5.1).

Formerly, pentacoordinate permutational isomers with a TBP skeleton were nomenclaturally characterized by defining some arbitrary isomer (*e.g.*, the most stable, or the first discovered) to be the reference isomer. Ligands are then numbered as a function of their skeletal position, *e.g.* as in *(4)*[5d,14,15], in an arbitrarily chosen spatial orientation. This results in what is called the "a" isomer[14] (or the "12"-isomer[5d] or the "21"-isomer[15], respectively) since the ligands L_1 and L_2 occupy the apical positions.

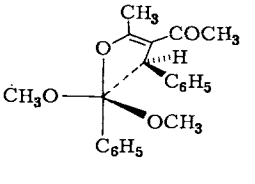


(4)

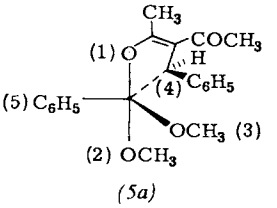
These "binary descriptors", in contrast to our permutational descriptors, do not represent the ligand or skeletal permutations that result from permutational isomerizations (*e.g.*, of the reference isomer). However, the binary descriptors have one distinct advantage: in the case of chiral isomers, the descriptors of antipodes can be immediately recognized as they are inverse symbols. Such nomenclature accounts for the TBP skeletal symmetry, but, if equivalent ligand sets exist, it yields different descriptors for the same molecule (see Table 1).



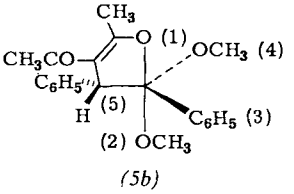
(5c)



(6)



(5a)



(5b)

The following discussion points out the latter shortcoming in some detail. If *(5)*[5a,b] is defined as the a-isomer or the 12-isomer respectively, the numbering of ligands is not unequivocally determined because of the skeletal symmetry; *(5a)*—*(5c)* can equally well serve for indexing the ligands. Independent of its spatial orientation *(5)* may be called the 12-isomer but the descriptors of its permutational isomers are found to be different due to the choice of *(5a)*, *(5b)*, or *(5c)* as the reference. For instance, *(6)* is the 15- or (because of the equivalent methoxy groups) the 51-isomer of *(5a)*; analogously *(6)* is simultaneously the 14- or 41-isomer of *(5b)* or *(5c)*.

3. The Bond System of Pentacoordinate Phosphorus

3.1. Quantum Mechanical Calculations

When treating the large systems we face in this study, one must make a reasonable compromise between the more accurate but far more rigorous and expensive *ab initio* methods and the less expensive semi-empirical calculations. The choice need not limit the usefulness of the data, since properly parametrized semi-empirical methods provide energies, geometries, dipole moments, bond orders, *etc.* that are in good agreement with experimental values.

Table 1. Comparison of the binary and permutational descriptors of pentacoordinate molecules with a TBP skeleton.

Binary descriptors			permutational descriptors									
Five different ligands $L_1,\ldots,L_5$												
[a]	[b]	[c]		$L_1=L_2$	$L_2=L_3$	$L_3=L_4$	$L_4=L_5$	$L_1=L_2$ $L_3=L_4$	$L_1=L_2$ $L_4=L_5$	$L_2=L_3$ $L_4=L_5$	$L_1=L_2$ $=L_3$	$L_2=L_3$ $=L_4$	$L_3=L_4$ $=L_5$
a	21	12	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 5)	(1 4)(2 5)
$\bar{a}$	12	$\bar{1}\bar{2}$	(1 4 2 5)	(1 4)(2 5)	(1 4)(3 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 4)(2 5)	(1 5)	(1 4)(2 5)
b	31	13	(1 4 3 5)	(2 4)(3 5)	(1 4)(2 5)	(1 4 5)	(1 4)(3 5)	(2 5)	(2 4)(3 5)	(1 4)(2 5)	(1 4)(2 5)	(1 5)	(1 4)
$\bar{b}$	13	$\bar{1}\bar{3}$	(1 4)(3 5)	(1 4)(3 5)	(1 4)(3 5)	(1 5)	(1 4)(3 5)	(1 5)	(2 4)(3 5)	(1 4)(2 5)	(1 4)(2 5)	(1 5)	(1 4)
c	41	14	(1 4 5)	(2 5)	(1 5)	(1 4 5)	(1 4)	(2 5)	(1 4)	(1 5)	(1 5)	(1 5)	(1 4)
$\bar{c}$	14	$\bar{1}\bar{4}$	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 5)	(1 4)
d	51	15	(1 4)	(1 4)	(1 4)	(1 4)	(1 4)	(1 4)	(1 4)	(1 5)	(1 4)	(1 4)	(1 4)
$\bar{d}$	15	$\bar{1}\bar{5}$	(1 4 2)	(2 4)	(1 4)	(1 4)	(1 5)	(1 4)	(1 5)	(1 5)	(1 4)	(1 4)	(1 4)
e	32	23	(2 4)(3 5)	(2 4)(3 5)	(2 4)(3 5)	(2 5)	(2 4)(3 5)	(2 5)	(2 4)(3 5)	(2 4)(3 5)	(1 4)(2 5)	(2 5)	(2 4)
$\bar{e}$	23	$\bar{2}\bar{3}$	(2 4 3 5)	(1 4)(3 5)	(2 4)(3 5)	(1 2 5)	(2 4)(3 5)	(1 5)	(2 4)(3 5)	(2 4)(3 5)	(1 4)(2 5)	(2 5)	(2 4)
f	42	24	(2 5)	(2 5)	(2 5)	(2 5)	(2 5)	(2 5)	(1 4)	(3 4)	(1 5)	(2 5)	(2 4)
$\bar{f}$	24	$\bar{2}\bar{4}$	(1 2 5)	(1 5)	(3 5)	(1 2 5)	(2 4)	(1 5)	(1 5)	(3 5)	(1 5)	(2 5)	(2 4)
g	52	25	(1 2 4)	(1 4)	(3 4)	(2 4)	(2 5)	(1 4)	(1 4)	(3 4)	(1 4)	E	(2 4)
$\bar{g}$	25	$\bar{2}\bar{5}$	(2 4)	(2 4)	(2 4)	(2 4)	(2 4)	(1 4)	(1 5)	(3 5)	(1 4)	E	(2 4)
h	43	34	(1 3 5)	(3 5)	(2 5)	(3 5)	(3 4)	(3 5)	(3 5)	(3 4)	(1 5)	(2 5)	E
$\bar{h}$	34	$\bar{3}\bar{4}$	(3 5)	(3 5)	(3 5)	(3 5)	(3 5)	(3 5)	(3 5)	(3 5)	(1 5)	(2 5)	E
i	53	35	(3 4)	(3 4)	(3 4)	E	(3 4)	E	(3 5)	(3 4)	(1 4)	E	E
$\bar{i}$	35	$\bar{3}\bar{5}$	(1 3 4)	(3 4)	(2 4)	(1 2)	(3 5)	E	(3 5)	(3 5)	(1 4)	E	E
j	54	45	E	E	E	E	E	E	E	E	E	E	E
$\bar{j}$	45	$\bar{4}\bar{5}$	(1 2)	E	E	(1 2)	E	E	E	E	E	E	E

[a] According to [14]; [b] according to [15]; [c] according to [5d].

These shortcomings are easily avoided by independent numbering of the skeletal and ligand positions. Such a procedure immediately affords an unambiguous, generally applicable definition for the reference isomer as well as the means for distinguishing between equivalent ligands. Detailed discussions of NMR data as well as graphical representation of some permutational isomerizations demand that these distinctions be unequivocal. Finally, it should be noted that where ligand equivalencies occur, nondistinguishable isomers have the same permutational descriptors (see Table 1). With five different ligands, the isomers are optical antipodes whose binary descriptors are inverse. In the presence of ligand equivalencies, however, only those pairs of mutually inverse binary descriptors which belong to distinguishable isomers relate to optical antipodes,

(*e.g.*, with $L_1 = L_2$: (1 4) – (2 4), (1 5) – (2 5), (1 4)(3 5) – (2 4)(3 5);
with $L_2 = L_3$: (2 4) – (3 4), (2 5) – (3 5), (1 4)(2 5) – (1 4)(3 5);
with $L_3 = L_4$: E – (1 2), (1 5) – (1 4 5), (2 5) – (1 2 5);
with $L_4 = L_5$: (1 4) – (1 5), (2 4) – (2 5), (3 4) – (3 5);
with $L_1 = L_2$ and $L_3 = L_4$: (1 5) – (2 5) and
with $L_2 = L_3$ and $L_4 = L_5$: (3 4) – (3 5).)

If the calculation method chosen is suitable for the system and is carefully employed, the errors generated by the approximations contained in the method will be small in magnitude and consistent in direction. Such results will adequately represent the trends within a wide range of real chemical systems and there is no loss of information essential to the validity of the interpretations and predictions one can make. Among the semi-empirical quantum mechanical methods available we chose to use the CNDO/2 (Complete Neglect of Differential Overlap) approximation[16,17].

While the details of the CNDO/2 method and its capabilities can be found in the original papers of *Pople et al.*[16] and recent reviews[17], we present a brief comment on the approximations made and the parametrization employed. In this approximation to the solution of the LCAO-SCF equations, only the valence electrons are treated explicitly by choosing a minimal set of basis functions (atomic orbitals) for a molecule in its ground state. The basis functions Φ_μ are treated as an orthonormal set, that is the overlap integrals $S_{\mu\nu}=\int\Phi_\mu\Phi_\nu=1$ are put to zero unless $\Phi_\nu=\Phi_\mu$ in which case they are unity. This results in the complete

neglect of differential overlap between atomic orbitals on the same atom. This approximation does not hold true in the case of orbitals of two different atoms, but it simplifies the calculation considerably without introducing serious errors. All two electron integrals which involve overlapping charge densities between different basis orbitals are likewise neglected so that the electron interaction integrals $\gamma_{\mu\nu}$ account for the repulsions between electrons on adjacent atoms. Approximations are also introduced to account for the effect of adjacent atomic cores upon an electron in any atomic orbital Φ_μ. Finally, approximation is made to calculate the effect of an electron in the field of two atoms simultaneously. The latter, termed a resonance integral β, is estimated by empirical values chosen to fit either experimental data or results obtained from *ab-initio* calculations.

The choice of parameterization (selection of basis functions) would include sp or spd alternatives. Fortunately, a comparison between the two exists for calculations on the bonding between some second and third row elements including PF_5 and SF_6[18]. In each case it was shown that inclusion of d-orbitals in the basis set of the third row ground state atom reduced bond polarity. Calculations on other species where dipole moments are known show that no reliable calculations are obtained without inclusion of d-orbitals for third row elements[7]. Although the question of d-orbital participation in ground state phosphorus is still open[19b, 20–24], d-orbitals were included in our universal basis set. This permits the extent of d-orbital participation to arise quite naturally. The implications of this will be discussed in some detail later on.

Extended Hückel MO calculations on phosphorus(v) halides have resulted in the impression that little d-orbital participation exists and therefore their effect may be neglected to a first approximation[24]. The most severe limitation of the extended Hückel method and the statements regarding d-orbitals that result concerns the choice of the optimum P-3d orbital exponent (Slater exponents)[21, 23]. *Slater*'s procedure for the calculation of screening constants from which one obtains the orbital exponents does not include the d-orbitals. Thus, one must assign an arbitrary value to the d-orbital exponent or determine it by some optimization procedure. In the HMO calculation above[24], the value of 1.0 was chosen for this exponent, which, as one might expect, yields a rather diffuse d-orbital set, predictably resulting in small d-orbital interactions. *Boyd* and *Lipscomb*[21] calculated a series of d-orbital exponents for phosphorus compounds, the optimum being 1.4. This value yields a more contracted d-orbital set, as is also to be expected if one considers the electrostatic field of a ligand set[22a]. In the CNDO/2 calculations a P-3d exponent of 1.6 is employed which approximates the value found by *Boyd* and *Lipscomb*.

Applications of the CNDO/2 method have recently appeared in similar attempts by *Segal et al.*[25] to discuss bonding and energy barriers to isomerization pathways. This rather elegant study revealed that small errors in the absolute values for energies and bond lengths are consistent and, within a given set of isomers, in the same direction.

It must be pointed out that, due to the approximations involving the atomic cores, comparison of the absolute values of various parameters, *e.g.* binding energy, between molecules is valuable only for molecules containing the same number and kind of atoms. Comparison between members of a particular isomer set are valid and lead to predictions of relative stability between isomers. Any comparison of energies between ground state geometries and presumed intermediate geometries must be done on species whose bond lengths and bond angles have been optimized for the lowest energy. In our calculations, bond lengths have been optimized to within less than ± 0.01 Å. An assumed D_{3h} trigonal bipyramidal symmetry was fixed for the pentacoordinate ground state phosphorus compounds. In the assumed geometries of the transition states and ring structures on the trigonal bipyramid, bond angles were optimized to within $\pm 0.5°$. No attempt was made to optimize the O—H or C—H bond distances since the contribution to the total energy was small relative to the calculation expense involved. P—H bond distances were optimized and showed a small energy change for a ± 0.05 Å variation about the equilibrium position.

3.2. Binding Energies of Phosphorane Derivatives[26]

Table 2 summarizes the absolute and relative binding energies (BE = Total Energy $-\Sigma$ Core Energies) of some pentacoordinate phosphorus compounds with the TBP skeleton *(2)*. The numbers *1*—*5* at the top of the table indicate the skeletal positions upon which the indicated ligands are placed. The data of Table 2 show that the BE is strongly influenced by the placement of the ligands, the more electronegative ($\approx$ apicophilic)[*] ligands preferring the apical positions (see Section 3.3.1) in agreement with the polarity rule[20, 27, 28]. Model compounds *(13)*—*(18)* (Table 2) have been "synthesized" by the computer, for, while the actual molecules are rather unlikely to exist, their relative BE data do permit one to draw conclusions pertinent to real systems, *e.g. (5)*, whose BE is not accessible because of the effort and expense of the computation required.

Again, while comparison of the absolute binding energies between different isomer sets is not informative, comparison of the relative BE of the members of a set of isomers lead to predictions for relative stabilities. The energetic preference for CH_3 to be equatorial is a trend predicted by the differences noted in *(10)* and *(16)*—*(18)*. The same trend is observed for the equatorial preference by $O^\ominus$ as calculated in *(14)*, *(15)* and *(17)*. The magnitude of the BE differences for $O^\ominus$ equatorial ($O^\ominus_e$) *vs* $O^\ominus$ apical ($O^\ominus_a$) seem relatively consistent in the three examples. In example *(17)* the sum of the relative BE for *(17b)* and *(17c)* are

[*] *Note added in proof*: Calculations done on the series PH_nF_{5-n} with and without d orbitals on the P basis set show an average reduction of electron density by 15% on P, an increase of 15% in bond lengths with an attendant reduction of BE by an order of magnitude when d orbitals are removed. The low energy isomer from PCl_2F_3 changes from diapical F—F to Cl—F when d orbitals are removed. This electronic behavior clearly indicates that reduction of polarity between phosphorus and its ligand set is accomplished by the back donation of electron density from the ligands *via* p orbitals into the empty d orbitals on phosphorus. This results in a 25—35% increase in stability.

Thus, the tendency for ligands to reside in apical positions might better be termed apicophilicity as d orbital effects, steric effects, and some function of electronegativity all combine to determine ligand position in the TBP.

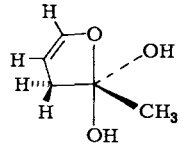
close to the relative BE shown for *(17d)*. Such comparisons demonstrate that the calculation is consistent within a wide range of molecules and indicates that the comparison of energy *differences* between isomer sets may be instructive.

of the ring is high. In the apical-equatorial placement of five-membered ring the overall strain is small. Furthermore, it is noteworthy that *(18b)* with an endocyclic apical P—C bond is considerably more stable than *(18c)* with an acyclic apical P—C bond.

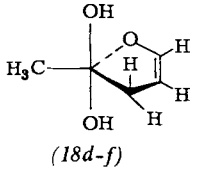
Table 2. Calculated BE of pentacoordinate phosphorus compounds.

Compound		Formula	Distribution of Ligands on Skeleton *(2)* 1	2	3	4	5	Absolute BE (kcal/mol)	Relative BE (kcal/mol)
(7)		PH_5	H	H	H	H	H	−412.5	0
(8)		PF_5	F	F	F	F	F	−606.1	0
(9)	*(a)*	PH_2F_3	F	H	H	F	F	−545.3	0
	(b)	PH_2F_3	F	F	H	F	H	−538.7	6.6 [29]
	(c)	PH_2F_3	F	F	F	H	H	−539.2	6.1
(10)	*(a)*	PF_4CH_3	F	F	CH_3	F	F	−1224	0
	(b)	PF_4CH_3	F	F	F	F	CH_3	−1185	39
(11)	*(a)*	PF_4CF_3	F	F	CF_3	F	F	−1326	0
	(b)	PF_4CF_3	F	F	F	F	CF_3	−1303	23
(12)	*(a)*	PF_4Cl	F	F	Cl	F	F	−617.7	0
	(b)	PF_4Cl	F	F	F	F	Cl	−583.1	34.6
(13)		$P(OH)_5$	OH	OH	OH	OH	OH	−1413	0
(14)	*(a)*	$P(OH)_4O^{\ominus}$	OH	OH	$O^{\ominus}$	OH	OH	−1307	0
	(b)	$P(OH)_4O^{\ominus}$	OH	OH	OH	OH	$O^{\ominus}$	−1279	28
(15)	*(a)*	$P(OH)_3(O^{\ominus})_2$	OH	$O^{\ominus}$	$O^{\ominus}$	OH	OH	−1027	0
	(b)	$P(OH)_3(O^{\ominus})_2$	OH	OH	$O^{\ominus}$	OH	$O^{\ominus}$	−995.2	31.8
	(c)	$P(OH)_3(O^{\ominus})_2$	OH	OH	OH	$O^{\ominus}$	$O^{\ominus}$	−982.2	44.8
(16)	*(a)*	$P(OH)_4CH_3$	OH	OH	CH_3	OH	OH	−2009	0
	(b)	$P(OH)_4CH_3$	OH	OH	OH	OH	CH_3	−1989	20
(17)	*(a)*	$P(OH)_3(O^{\ominus})CH_3$	OH	$O^{\ominus}$	CH_3	OH	OH	−1904	0
	(b)	$P(OH)_3(O^{\ominus})CH_3$	OH	OH	CH_3	OH	$O^{\ominus}$	−1872	32
	(c)	$P(OH)_3(O^{\ominus})CH_3$	OH	OH	$O^{\ominus}$	OH	CH_3	−1882	22
	(d)	$P(OH)_3(O^{\ominus})CH_3$	OH	OH	OH	$O^{\ominus}$	CH_3	−1853	51
(18)	*(a)*	$P(OH)_2(OCHCHCH_2)CH_3$	OH	CH_3	CH_2CHCHO		OH	−3793	0
	(b)	$P(OH)_2(OCHCHCH_2)CH_3$	OH	CH_3	$OCHCHCH_2$		OH	3773	20
	(c)	$P(OH)_2(OCHCHCH_2)CH_3$	OH	OH	CH_2CHCHO		CH_3	−3756	37
	(d)	($\alpha = 114°$)	$OCHCHCH_2$		CH_3	OH	OH	−3753	40
	(e)	($\alpha = 102°$)	$OCHCHCH_2$		CH_3	OH	OH	−3750	43
	(f)	($\alpha = 90°$)	$OCHCHCH_2$		CH_3	OH	OH	−3749	44

For instance, the BE data of *(18)* indicate that, in a cyclic oxyphosphorane derivative, a five-membered ring prefers apical-equatorial placement, again in accord with qualitative experimental observation. It is interesting to note that the BE of *(18d—18f)* with a diequatorial ring is, un-



(18a)



(18d-f)

expectedly (see Ref. [5a] and footnote 11 therein), only slightly dependent upon the magnitude of the endocyclic C—P—O angle α; with small α (~90°) the diequatorial C—P—O strain is large but the rest of the ring is only slightly strained, whereas with large α (~114°) the C—P—O strain is low while the strain in the remainder

Comparison of our data with electron diffraction studies[19a] indicate that the CNDO/2 calculated equilibrium bond lengths for the ground state are overestimated by 5—6%. This is probably due to inaccurate estimation of the β values assigned to the core Hamiltonian; the β values could be altered to fit experiments more closely, but the gain in accuracy would not provide any new or more reliable information since all systems investigated are similarly affected.

3.3. Participation of the P-3d Orbitals in the Bond System

In this section, an attempt is made to call attention to those features of the P-bond system which are of particular interest regarding the problems central to this paper with no claim of a comprehensive theoretical treatment of the bonding in phosphorus compounds[26].

Investigation of the electron densities assigned by the CNDO/2 calculation yields an interesting trend in the comparison between electronic charge distribution for

Table 3. Charge distribution in *(9)*.

Z, L	*(9a)* F, F-a	*(9b)* F, H-a	*(9c)* H, H-a
P	4.2094	4.1085	4.2003
F	7.2249e	7.2345e	7.2571e
F	7.2776a	7.2345e	7.2571e
F	7.2776a	7.2512a	7.2571e
H	1.0053e	1.0290e	1.0142a
H	1.0053e	1.0703a	1.0142a

a = apical; e = equatorial. Z = central atom; L = ligand.

Table 4. Charge distribution in *(18a)* and *(18b)*.

Z, L	*(18a)* CH_3-e OH-a $H_2CCHCHO$	*(18b)* CH_3-e OH-a $OCHCHCH_2$
P	4.5352	4.5148
OH	6.2846e	6.2922e
OH	6.3700a	6.3250a
OCH	6.3061a	6.2558e
CH_2	4.0683e	4.1180a
CH_3	4.1378e	4.1335e

Table 5. Charge distribution in *(17a)*—*(17d)*.

Z, L	*(17a)* CH_3, O^--e	*(17b)* CH_3, O^--e, a	*(17c)* CH_3, O^--a, e	*(17d)* CH_3, O^--a
P	4.5696	4.5592	4.5660	4.5598
OH	6.3354e	6.3386e	6.3442e	6.3579e
OH	6.3630a	6.3499e	6.3487e	6.3579e
OH	6.3630a	6.3803a	6.3785a	6.3579e
O^-	6.4583e	6.5526a	6.4937e	6.5220a
CH_3	4.1408e	4.1345e	4.1489a	4.1618a

stabilization of the various isomers we investigated. This is not intended to be a rigorous treatment of the bonding in pentacoordinate phosphorus compounds[26] as our original intention was to provide a framework of understanding for isomerization processes. However, certain interesting possibilities should be pointed out at this time due to the nature of the controversy.

Table 6 is an extract from the density matrix of the program for PF_5. The diagonal elements correspond to electron densities within the prescribed orbital. The sum of these elements is equal to the total valence shell electron density for phosphorus, $\Sigma_P = 3.8890$. Of this, 1.3671 units of electron charge are shown to reside in the five P 3d-orbitals, approximately 35% of the total density. Table 7 is a listing of the off-diagonal matrix elements (italics) which represent the bond orders or resonance integrals of the core Hamiltonian operator. The negative product of these is the stabilizing contribution of the particular ligand orbital with the phosphorus 3 d-orbitals. Tables 8 and 9 are the P 3d-orbital density matrices for *(14a)* and *(14b)* respectively, while Tables 10 and 11 are analogous to Table 7. The total phosphorus electron density difference between the two isomers is 0.044 units; the difference in electron density in the d-orbitals of *(14a)* and *(14b)* is 0.011 units. Approximately 25% of the difference in electron charge takes place *via* the phosphorus d-orbitals. From Tables 10 and 11 one obtains the orbital bond energy contribution difference of 0.0179 a.u., which is equivalent to 30% of the change in binding energy for the two isomers. These results lend strong support to the notion that certain isomers of phosphorus(v) compounds are

Table 6. Extract from the density matrix of the calculation for PF_5 *(8)*.

				1	2	3	4	5	6	7	8	9
1	1	P	S	1.0255	−0.0000	0.0000	0.0000	0.0119	−0.0000	0.0000	0.0000	0.0000
2	1	P	PX	−0.0000	0.4639	−0.0000	−0.0000	−0.0000	−0.0000	−0.0000	0.1416	0.0000
3	1	P	PY	0.0000	−0.0000	0.4639	0.0000	0.0000	−0.0000	0.0000	0.0000	−0.1416
4	1	P	PZ	0.0000	−0.0000	0.0000	0.5685	−0.0000	−0.0000	0.0000	0.0000	0.0000
5	1	P	DZ2	0.0119	−0.0000	0.0000	−0.0000	0.4303	0.0000	−0.0000	−0.0000	−0.0000
6	1	P	DXZ	−0.0000	−0.0000	−0.0000	−0.0000	0.0000	0.2150	0.0000	−0.0000	0.0000
7	1	P	DYZ	0.0000	−0.0000	0.0000	0.0000	−0.0000	0.0000	0.2150	−0.0000	−0.0000
8	1	P	DX-Y	0.0000	0.1416	0.0000	0.0000	−0.0000	−0.0000	−0.0000	0.2534	−0.0000
9	1	P	DXY	0.0000	0.0000	−0.1416	0.0000	−0.0000	0.0000	−0.0000	−0.0000	0.2534
10	2	F	S	0.1565	0.2693	0.0000	0.0000	−0.1457	−0.0000	0.0000	0.2319	0.0000
11	2	F	PX	−0.4386	−0.5290	−0.0000	−0.0000	0.2332	0.0000	−0.0000	−0.3082	0.0000
12	2	F	PY	−0.0000	0.0000	0.2585	−0.0000	−0.0000	0.0000	−0.0000	0.0000	0.3606
13	2	F	PZ	−0.0000	−0.0000	−0.0000	0.1357	−0.0000	0.3217	−0.0000	0.0000	−0.0000

phosphorus *vs* the ligand and the binding energy of the molecule. For every example in Table 2, the difference in electron density between phosphorus and the average electron density of the ligand set is lower for the lower energy isomer. Tables 3—5 reproduce the electron densities calculated for phosphorus and its ligands in a representative sample of cases. Further, notice that in each case, electron density on phosphorus in greater for the low energy isomer. It seems clear from this correlation that an increase in stability is gained by virtue of the phosphorus atom receiving some electron density possessed by the ligands. The suggestion[18, 19, 22a] that third row elements may be stabilized by back donation of electron density into the vacant d-orbitals on phosphorus tempted us to speculate upon the extent of d-orbital participation in the stabilized by passing electron density into the d-orbitals on the central atom. The calculations predict that an apical ligand must carry more electron charge than its equatorial counterpart, an experimentally observed reality[19b]. Further, the CNDO/2 program predicts greater double bond character in the equatorial bonds and bond shortening in the equator relative to the apical positions. The calculation also predicts equatorial methyl group participation [cf. *(10)* and *(16)*—*(18)*] with d_{z^2} orbitals on phosphorus which might be an interesting example of "inverse" hyperconjugation where the positive linear combination of atomic hydrogen orbitals produces an orbital with the proper symmetry for combination with the d_{z^2} orbital, having a node in the plane of the d_{z^2} negative doughnut.

Our bonding model then predicts substantial phosphorus d-orbital participation, which also appears to play a substantial role in the determination of ligand position on the trigonal bipyramidal skeleton.

contain two different types of substituents. BE contributions from the P 3d orbitals in a diapical X-P-Y system or a diequatorial X-P-Y_2 system respectively are generally lower than the mean value for X-P-X and Y-P-Y diapical

Table 7. Bond orders (above) and resonance integrals of core Hamilton operators (below, *italic*) of PF_5 ($\Sigma_P = 3.8890$).

F-Orbital	P-Orbital	d_{z^2}	d_{xz}	d_{yz}	$d_{x^2-y^2}$	d_{xy}	Energy Contribution (a. u.)
F 4, 5	s	0.2719 *−0.2421*					−0.0658
	p_x		0.3380 *−0.1190*				−0.0402
	p_y			0.3380 *−0.1190*			−0.0402
	p_z	−0.3877 *0.1420*					−0.0550
	$\Sigma_F = 7.2396$					Sum	−0.2013
F 1, 2, 3	s	−0.1457 *0.1210*			−0.1160 *0.1048*	−0.2009 *0.1815*	−0.0662
	p_x	−0.1166 *0.0355*			−0.3475 *0.1200*	0.0227 *0.0018*	−0.0457
	p_y	0.2020 *−0.0615*			−0.0227 *−0.0018*	0.3213 *−0.1220*	−0.0516
	p_z		−0.1609 *0.0595*	0.2786 *0.1030*			−0.0382
	$\Sigma_F = 7.2106$					Sum	−0.2017

Table 8. P-3d density matrix of *(14a)* ($\Sigma_d = 1.7893$).

P	DZ 2	*0.4864*	0.0009	0.0058	0.0137	−0.0215
P	DXZ	0.0009	*0.3079*	0.0164	0.0016	−0.0056
P	DYZ	0.0058	0.0164	*0.3081*	0.0055	−0.0017
P	DX-Y	0.0137	0.0016	0.0055	*0.3652*	0.0367
P	DXY	−0.0215	−0.0056	−0.0017	0.0367	*0.3217*

Table 9. P-3d density matrix for *(14b)* ($\Sigma_d = 1.7781$).

P	DZ 2	*0.5017*	0.0011	0.0013	0.0054	0.0136
P	DXZ	0.0011	*0.3468*	−0.0043	0.0168	0.0011
P	DYZ	0.0013	−0.0043	*0.3415*	0.0064	−0.0174
P	DX-Y	0.0054	0.0168	0.0064	*0.3121*	0.0085
P	DXY	0.0136	0.0011	−0.0174	0.0085	*0.2762*

Although the evidence is far from complete the following generalizations might be drawn:

3.3.1. Apical positions produce less P 3d-orbital interaction than the equatorial ones; therefore, atoms in apical positions must be able to support more electronic charge on themselves since back donation of charge is less likely. Conversely, equatorial positions offer the greatest d-orbital interaction; consequently, less electronegative atoms and anions preferentially occupy these sites [cf. *(14)—(17)*].

3.3.2. An overall weakening of the bond system occurs when either the apical or equatorial ligand subsets or PX_3 and PY_3 equatorial systems [see *(9)*]. This effect is more pronounced for the equatorial system.

The statement 3.3.1 corresponds to the polarity rule[20, 27, 28] which was postulated without consideration of the d-orbitals and 3.3.2 indicates one of the limitations of this rule, which is further limited by its neglect of ligand-ligand interactions (see Section 4.2.4 and note added in proof p. 691).

4. Regular and Irregular Processes

4.1. General Criteria

Pentacoordinate compounds undergo regular and irregular rearrangement processes. Regular processes proceed without rupture and reformation of bonds while this is not true for the irregular process. Intermediates of irregular rearrangements differ in coordination number relative to starting material and products. If bonds are first cleaved and then reformed, the intermediates are lower in coordination number compared to the initial phosphorane while in the event that bonds are formed first, then cleaved, intermediates possess higher coordination numbers. Rearrangements previously interpreted by invoking the BPR mechanism, with few exceptions[30], certainly proceed by regular processes. Thus, an alternative to the BPR mechanism must correspond to a regular process.

The aforementioned regular rearrangement process proceeding with preservation of coordination number is a

Table 10. Bond orders (above) and resonance integrals of core Hamilton operators (below, *italic*) of *(14a)* ($\Sigma_P = 4.4677$).

O-Orbital	P-Orbital	d_{z^2}	d_{xz}	d_{yz}	$d_{x^2-y^2}$	d_{xy}	Energy Contribution (a. u.)
OH 4, 5	s	0.3341 *−0.2480*					−0.0829
	p_x		−0.3673 *0.1554*				−0.0571
	p_y			−0.3042 *0.1554*			−0.0473
	p_z	0.3790 *−0.1287*					−0.0487
	$\Sigma_O = 6.3600$					Sum	−0.2360
OH 1, 2	s	−0.1686 *0.1240*			0.2810 *−0.2148*		−0.0812
	p_x	0.1994 *−0.0643*			−0.2823 *0.1114*		−0.0442
	p_y					0.3144 *−0.1554*	−0.0488
	p_z		0.3634 *−0.1554*				−0.0564
	$\Sigma_O = 6.3580$					Sum	−0.2306
O^- 3	s	−0.1590 *0.1240*			−0.1288 *0.1074*	0.2262 *−0.1860*	−0.0756
	p_x	−0.1170 *0.0322*			−0.4915 *0.1444*	−0.1513 *0.0190*	−0.0776
	p_y	−0.1927 *0.0557*			0.1327 *−0.0190*	0.3382 *−0.1224*	−0.0546
	p_z		−0.2385 *0.0777*	−0.4111 *0.1346*			−0.0738
	$\Sigma_O = 6.4921$					Sum	−0.2816

Table 11. Bond orders (above) and resonance integrals of core Hamilton operators (below, *italic*) of *(14b)* ($\Sigma_P = 4.4236$).

O-Orbital	P-Orbital	d_{z^2}	d_{xz}	d_{yz}	$d_{x^2-y^2}$	d_{xy}	Energy Contribution (a. u.)
O^- 5	s	0.3011 *−0.2480*					−0.0746
	p_x		−0.4953 *0.1554*				−0.0769
	p_y			−0.5008 *0.1554*			−0.0778
	p_z	0.3425 *−0.1287*					−0.0440
	$\Sigma_O = 6.5341$					Sum	−0.2733
OH 4	s	0.3133 *−0.2480*					−0.0776
	p_x		0.3506 *−0.1554*				−0.0544
	p_y			0.2961 *−0.1554*			−0.0460
	p_z	−0.3378 *0.1287*					−0.0434
	$\Sigma_O = 6.3734$					Sum	−0.2214
OH 1, 2, 3	s	−0.1957 *0.1240*			−0.1955 *0.1074*	−0.2020 *0.1860*	−0.0828
	p_x	−0.1111 *0.0322*			−0.2958 *0.1444*	−0.0040 *−0.0190*	−0.0461
	p_y	0.2293 *−0.0557*			−0.0449 *0.0190*	0.2973 *−0.1224*	−0.0501
	p_z		−0.1789 *0.0777*	0.3063 *−0.1346*			−0.0552
	$\Sigma_O = 6.3629$					Sum	−0.2342

concept of far reaching consequence in chemistry. This allows one to state with precision some important classifications and definitions, which, for a long period, have proved useful in chemistry.

4.2. Molecules with Rigid and Flexible Skeletons

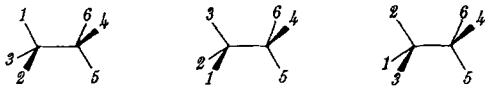
4.2.1. Dynamic Symmetry

The interconversion of permutational isomers by regular processes is possible only if the molecular skeleton involved is flexible, *i.e.* if the molecular skeleton can be represented by some rigid models with numbered positions which themselves can be interconverted with preservation of the coordination numbers of all skeletal centers by deformation of bond angles or by rotations about bonds. Some valence isomerizations may also be thought of as proceeding with preservation of coordination number. An instance of monocentric skeletal flexibility is the numbered TBP model *(2)*, which is transformed by certain bond angle deformations (*e.g.* BPR or TR) with preservation of coordination number 5 into other, equivalent renumbered TBP skeletons. The dicentric skeletal model ethane, *(19a)*, on the other hand, is converted into other corresponding rigid skeletal models *(19b)* and *(19c)* by rotation about the C—C bond conserving both coordination number 4 and all bond angles at both centers.

Equivalencies of skeletal positions arise not only from the symmetry of the rigid skeletal models but also from the skeletal flexibility. Just as one can represent rigid skeletal symmetry by permutation groups $G \subset S_n$, the rigid skeletal equivalence groups, one can also represent the additional equivalencies arising from skeletal flexibility by permutation groups $F \subset S_n$. We employ the term *dynamic skeletal symmetry* for the symmetry of a flexible molecular skeleton which is given by the symmetry of the rigid skeletal models and their interconvertibility by flexibility operations. Dynamic skeletal symmetry is a permutational symmetry which does not yield itself to geometric interpretation in all cases. Often there is no rigid geometric model of corresponding symmetry.

In order that one be able to interpret the properties of nonrigid symmetrical molecules, such as ammonia or methyldifluoroborane, *Longuet-Higgins*[6] introduced the *total molecular symmetry* concept. This comprised all permutational ligand equivalencies in the molecule as well as those due to the symmetries of the rigid molecular models and those due to flexibility. The symmetry of the molecules discussed by *Longuet-Higgins* originates in their skeletal symmetry which corresponds to the molecular symmetry if the necessary ligand equivalencies exist. If one now detaches the ligand set and considers only the skeletal properties of the molecule, one is led from the total molecular symmetry argument to dynamic skeletal symmetry which is independent of the ligand set, existing in molecules possessing skeletal symmetry but actually asymmetric due to ligand inequivalencies.

The dynamic symmetry of a molecular skeleton is in general represented by the product of the skeletal equivalence group G and the skeletal flexibility group F, *i.e.* $D = G \times F \subset S_n (g \leqslant d \leqslant n!)$. This concept is illustrated by the example employing an ethane skeleton *(19)*.



(19a) *(19b)* *(19c)*

The symmetries of molecules *(19)* are described by the skeletal equivalence group

$$G = \{E,\ (1\,2\,3)(4\,5\,6),\ (1\,3\,2)(4\,6\,5),\ (1\,4)(2\,6)(3\,5),\ (1\,5)(2\,4)(3\,6),\ (1\,6)(2\,5)(3\,4)\} \quad (6)$$

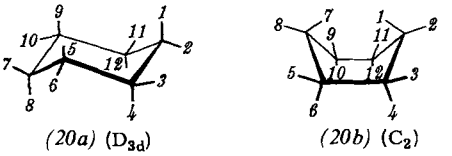
of the order g = 6 and the flexibility which is given by the interconversions of the rigid skeletal models *(19a)*, *(19b)*, and *(19c)* and described by

$$E = \{E,\ (1\,2\,3),\ (1\,3\,2)\} \quad (7)$$

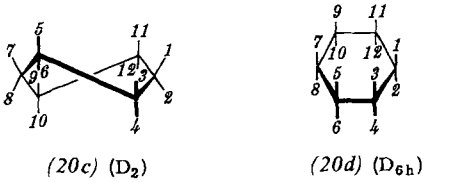
the skeletal flexibility group of the order f = 3. The group product

$$\begin{aligned} D = G \times F = \{&E,\ (1\,2\,3),\ (1\,3\,2),\ (4\,5\,6),\ (4\,6\,5),\ (1\,2\,3)(4\,5\,6),\\ &(1\,2\,3)(4\,6\,5),\ (1\,3\,2)(4\,5\,6),\ (1\,3\,2)(4\,6\,5),\\ &(1\,4)(2\,6)(3\,5),\ (1\,5)(2\,4)(3\,6),\ (1\,6)(2\,5)(3\,4),\\ &(1\,4\,2\,6\,3\,5),\ (1\,4\,3\,5\,2\,6),\ (1\,5\,2\,4\,3\,6),\\ &(1\,5\,3\,6\,2\,4),\ (1\,6\,2\,5\,3\,4),\ (1\,6\,3\,4\,2\,5)\} \end{aligned} \quad (8)$$

of the order d = 3 × 6 = 18 represents the *dynamic symmetry* of the ethane skeleton *(19)*, a permutational symmetry for which there is no isomorphic point group symmetry. If six different ligands are attached to the rigid skeleton *(19a)*, then 6! = 720 mappings of the ligand set onto the set of skeletal positions are possible and six (= g) each of these are equivalent due to the skeletal symmetry leading to 120 distinguishable permutation isomers. Now, introducing skeletal flexibility F leads to the further equivalence of 3 (= f) each of these such that the distinguishable isomers are reduced to 40. This is equivalent to the statement that there are 40 isomeric ethane derivatives, each of these having 3 conformers.



(20a) (D_{3d}) *(20b)* (C_2)



(20c) (D_2) *(20d)* (D_{6h})

With cyclic molecular skeletons, however, it is possible to construct skeletal models *(e.g. (20d))* which have a geometric (point group) symmetry equivalent to the dynamic skeletal symmetry.

It is interesting to note that for *(20a)*, *(20b)*, and *(20c)*, G and F are different for each but yield the same product D in all cases. At the same time D corresponds to the rigid skeletal symmetry of *(20d)* and the dynamic symmetry of *(20)*. In such cases, dynamic symmetry is sometimes incorrectly interpreted as geometrical symmetry, being called the time average symmetry or the maximum possible symmetry of *(20)*[1].

4.2.2. Generalization of the Conformer Concept

If the flexibility F of the TBP skeleton *(2)* is represented by permutations reflecting the equivalence of skeletal positions achieved by TR or BPR processes, the dynamic symmetry here comprises all 5! permutations of the symmetric group S_5. Here, the dynamic symmetry of the TBP skeleton corresponds to a complete symmetry equivalence of all skeletal positions. Such a state is permutationally representable but cannot be geometrically realized as it is impossible to construct a regular three dimensional figure with five equivalent vertices.

For a TBP molecule with 5 different ligands there are 20 conformers (see Section 4.2.3) but only one isomer. By reducing the flexibility of *(2)* one obtains only two isomers (see Graph 6) with three or six conformers respectively.

For an example relevant to this discussion we turn to the case of bullvalene[31]. The observed equivalence of all ten CH groups in this molecule when positional exchange occurs *via* valence isomerization may be considered a special type of skeletal flexibility. It is not possible to find any geometric arrangement in which all CH groups of bullvalene would, in an "instantaneous view", occupy symmetry equivalent positions. This is why bullvalene cannot be "aromatic".

Molecules differing only by permutations of equivalent ligands and/or permutations at such skeletal sites that are equivalent with reference to the *dynamic skeletal symmetry* belong to the same "isolable" isomers or *classical species*[12]. If instead the equivalence of the skeletal positions is related to the *rigid skeletal symmetry*, the molecules belong, in an analogous manner, to the *same conformer*.

We propose to use conformer as a collective term comprising the concepts of the *rotamer* and the *flexomer*. Often a clear distinction between these two species is not possible. Rotamer is used to describe those permutational isomers which, in the idealized case, are interconverted by such skeletal deformations of polycentric skeletons where only dihedral angles are changed without significant change of the bond angles at the skeletal centers. Those permutational isomers called flexomers are interconverted by skeletal motions deforming bond angles at one or more skeletal centers.

Hence, the conformers of a classical species are the distinguishable permutational isomers which are interconverted by regular processes (represented by the permutations of the skeletal flexibility group F) whereas the classical species which refer to the flexible skeletal model are interconverted only by irregular processes[12].

Also, it is both possible and useful, *e.g.*, for the discussion of the Wagner-Meerwein rearrangement, to define an *irregular dynamic skeletal symmetry* where not only the permutations of the skeletal flexibility groups F are included but the skeletal transformations by irregular processes as well.

There are molecules for which some distinguishable conformers vanish in certain temperature ranges while still other conformational differentiation is possible due to some motion belonging to the skeletal flexibility. This is represented by a subgroup F^* of the skeletal flexibility group F. An example might be a methylcyclohexane with a rotating methyl group which does not stop between the rotational barriers, while the axial *vs* equatorial placement of the rotating methyl group and the cyclohexane skeleton *(20a)* is still distinguishable. In such cases the conformers relate to the *partially* dynamic skeletal symmetry ($D^* = G \times F^*$) instead of the rigid skeletal symmetry.

Extension of the conformer concept, as developed above, is useful not only for the present topic but also for the purpose of viewing related phenomena from a common viewpoint.

4.2.3. Stereochemical Quantum Numbers

The classical species and their conformers within an isomer class possessing n skeletal sites, a rigid skeletal equivalence group G and a flexibility group F, are obtained from the reference isomer $\mathbf{M}_{0,0}$ by permutations corresponding to the products of the descriptors of the classical species P_σ or Q_σ and the elements of F (see Table 12). The columns of Table 12 (σ = const.) contain the conformers of the isomers $\mathbf{M}_\sigma$, and the rows (κ = const.) the analogous conformers of the different isomers. It follows that σ and κ then serve the purpose of "stereochemical quantum numbers"[12], σ being the isomer and κ the conformer quantum number.

Table 12. Systems of isomers and their conformers.

κ \ σ	0	1	2		i-1
0	$M_{0,0}$	$M_{1,0}$	$M_{2,0}$		$M_{i-1,0}$
1	$M_{0,1}$	$M_{1,1}$	$M_{2,1}$		$M_{i-1,1}$
2	$M_{0,2}$	$M_{1,2}$	$M_{2,2}$		$M_{i-1,2}$
j-1	$M_{0,j-1}$	$M_{1,j-1}$	$M_{2,j-1}$		$M_{i-1,j-1}$

Using a rigid skeletal model with n sites and n different ligands along with a rigid skeletal equivalence group G one obtains from $\mathbf{M}_{0,0}$ n!/g distinguishable permutation isomers. If one further considers the flexibility of the skeleton, a total of i = n!/d "isolable" isomers ($\mathbf{M}_0, \ldots, \mathbf{M}_{i-1}$), called the classical species of this class of permutation isomers, result from the reference "isolable isomer". The descriptor of the latter coincides with the descriptor of $\mathbf{M}_{0,0}$. Descriptors P_σ or Q_σ of these "classical species" correspond to the descriptors $P_{\sigma,0}$ or $Q_{\sigma,0}$ of the reference conformers $\mathbf{M}_{0,0}, \mathbf{M}_{1,0}, \ldots, \mathbf{M}_{i-1,0}$ (see first row of Table 12) of the "isolable" isomers of $\mathbf{M}_0$.

The l and s-descriptors of the κ^{th} conformer of the σ^{th} isomer $\mathbf{M}_{\sigma,\kappa}$ (σ^{th} column, κ^{th} row of Table 12) are generated by eq. (9).

$$\begin{pmatrix} l \\ s \end{pmatrix}_{\sigma,\kappa} = \begin{pmatrix} \boldsymbol{P}_{\sigma,0}\ n \\ \boldsymbol{Q}_{0,\kappa}\ n \end{pmatrix} = \begin{pmatrix} \boldsymbol{Q}_{0,\kappa}^{-1} \times \boldsymbol{P}_{\sigma,0}\ n \\ n \end{pmatrix} = \begin{pmatrix} n \\ \boldsymbol{P}_{\sigma,0}^{-1} \times \boldsymbol{Q}_{0,\kappa}\ n \end{pmatrix} \tag{9}$$

when $\boldsymbol{P}_{\sigma,\kappa} = \boldsymbol{P}_{0,\kappa} \times \boldsymbol{P}_{\sigma,0}$ or $\boldsymbol{Q}_{\sigma,\kappa} = \boldsymbol{Q}_{\sigma,0} \times \boldsymbol{Q}_{0,\kappa}$.

When one represents the conformational interconversions of a flexible skeleton by a graph, this graph applies to all columns of Table 12 simultaneously and, due to skeletal properties, is independent of the individual distributions of the ligands which are related to the dynamic skeletal symmetry. For example, Graph 5 describes the conformational interconversions of two isomers with a TBP skeleton by the $(TR)^2$ mechanism. These isomers themselves are not interconverted if $(TR)^2$ is the only rearrangement mechanism considered.

If some of the ligands are equivalent, the conformers are representatives of the double cosets[11] of $\boldsymbol{H}$ and $\boldsymbol{G}$; the classical species represent double cosets of $\boldsymbol{H}$ and $\boldsymbol{D}$. In this case, some of the permutation isomers of Table 12 are equivalent because of ligand equivalencies ($\mathbf{M}_{\sigma,\kappa} = \mathbf{M}_{\sigma',\kappa'}$). It can happen that skeletal flexibility not only depends upon the molecular skeleton itself but upon other factors as well, *e.g.* special interactions between individual ligands and temperature.

Particularly strong inter-ligand interactions (ring formation, see Graph 5; hydrogen bonds, bulky groups, *etc.*) may result in the disappearance of some of the conformers $\mathbf{M}_{\sigma,\kappa}$ of $\mathbf{M}_{\sigma}$ (see Ref. 12). The same consequence is observed for the particularly strong preference some ligands show for certain skeletal positions.

4.2.4. Measurable Properties of Permutation Isomers

An equation (10), that permits one to compute the values of some observable parameters $O_{0,0}$ (*e.g.* energy values, equilibrium concentrations, chirality observations, *etc.*) for the reference conformer $\mathbf{M}_{0,0}$ as a function of the ligand set L and its distribution on the skeleton, is transformed into eq. (11) for the corresponding observable $O_{\sigma,\kappa}$ of the permutation isomer $\mathbf{M}_{\sigma,\kappa}$ by the descriptor $\boldsymbol{P}_{\sigma,\kappa}$ of the conformer.

$$O_{0,0} = O_{0,0}(L_1, \ldots, L_n) \tag{10}$$

$$O_{\sigma,\kappa} = \boldsymbol{P}_{\sigma,\kappa} O_{0,0}(L_1, \ldots, L_n) = O_{0,0}(\boldsymbol{P}_{\sigma,\kappa}\{L_1, \ldots, L_n\}) \tag{11}$$

As an example, the approximation [eq. (12)] of the energy $\mathfrak{E}_{0,0}$ of the reference conformer leads (by pairwise interactions) to eq. (13) for its permutation isomer $\mathbf{M}_{\sigma,\kappa}$. $\mathfrak{E}_s(\gamma_i, \lambda_i)$ in eqs. (12) and (13) is a function of the ligand L_i

$$\mathfrak{E}_{0,0} = \sum_i \mathfrak{E}_s(\gamma_i, \lambda_i) + \sum_{\substack{i,j \\ (i \neq j)}} \mathfrak{E}_1(\gamma_i, \gamma_j, \lambda_i, \lambda_j) \tag{12}$$

$$\mathfrak{E}_{\sigma,\kappa} = \boldsymbol{P}_{\sigma,\kappa}\left(\sum \mathfrak{E}_s(\gamma_i, \lambda_i) + \sum \mathfrak{E}_1(\gamma_i, \gamma_j, \lambda_i, \lambda_j)\right) \tag{13}$$

(with parameters λ_i and λ_i') and the i^{th} skeletal position (with parameters γ_i and γ_i'). $\mathfrak{E}_1(\gamma_i', \gamma_j', \lambda_i', \lambda_j')$ describes the interaction of the ligands L_i and L_j. The l-descriptor $\boldsymbol{P}_{\sigma,\kappa}$ permutates the indices of the ligand parameter λ and λ' only, and not the indices of the skeletal parameters γ and γ'.

For molecules with a TBP skeleton *(2)* one can approximate eq. (12) with polynomials of the lowest degree and, considering only the interactions of nearest neighbor, one obtains eq. (14).

$$\begin{aligned} \mathfrak{E}_0 = {} & \gamma_e(\lambda_1+\lambda_2+\lambda_3) + \gamma_a(\lambda_4+\lambda_5) + \\ & + \gamma_{ee}(\lambda_1'\lambda_2' + \lambda_1'\lambda_3' + \lambda_2'\lambda_3') + \gamma_{ae}(\lambda_1'+\lambda_2'+\lambda_3')(\lambda_4'+\lambda_5') \end{aligned} \tag{14}$$

Here, γ_e, γ_a, γ_{ee}, and γ_{ae} are skeletal parameters whose indices a and e relate to the apical and equatorial skeletal positions. One can see from this simple approximation (eq. (14)) that qualitative rules of the type represented by the polarity rule[20, 27, 28] (see Section 3.3.1) have only limited value if the stability of the species in question has been determined considering only one type of interaction.

Approximations of the above type seem to be well suited for the treatment of the conformational problems of molecules with polycentric skeletons, *e.g.* the ethane *(19)* or cyclohexane skeleton *(20)*. In general, one is interested in the energy differences $\Delta\mathfrak{E} = \mathfrak{E}_{\sigma,\kappa} - \mathfrak{E}_{\sigma',\kappa'}$ of two conformers such that the energy contribution from ligand interaction with the skeleton may be neglected as this is approximately the same for all conformers. Thus it suffices to consider just the pairwise interactions between neighboring ligands. The energy difference between conformers is given by eq. (15) where the first two indices of $\mathfrak{E}_{ij,ij}$ refer to the i^{th} and j^{th} skeletal positions and the last two to the ligands L_i and L_j.

$$\mathfrak{E}_{\sigma,\kappa} - \mathfrak{E}_{\sigma',\kappa'} = (\boldsymbol{P}_{\sigma,\kappa} - \boldsymbol{P}_{\sigma',\kappa'})\mathfrak{E}_{0,0} = (\boldsymbol{P}_{\sigma,\kappa} - \boldsymbol{P}_{\sigma',\kappa'}) \sum_{\substack{i,j \\ (i \neq j)}} \mathfrak{E}_{i,j,i,j} \tag{15}$$

5. Formal Classification of the Rearrangement Processes of Pentacoordinate Molecules

5.1. Isomerizers

The reference isomer *(1)* $\equiv \mathbf{M}_0$ and its matrix representation $\begin{pmatrix} l \\ s \end{pmatrix}_0$ are distinguishable by the fact that for $\mathbf{M}_0$ the ligand and skeletal indices l and s behave like contravariant variables. This is to say that the transformation of $\mathbf{M}_0$ into its permutation isomer $\mathbf{M}_\sigma$ is equally well represented by either the ligand permutation $\boldsymbol{P}_\sigma$ or the skeletal permutation $\boldsymbol{Q}_\sigma$ (see eq. (1)) where $\boldsymbol{Q}_\sigma$ is numerically equivalent to $\boldsymbol{P}_\sigma^{-1}$. The latter operator is obtained from $\boldsymbol{P}_\sigma$ by inverting the sequence of its digits. If $\boldsymbol{P}_\sigma = (1\ 2\ 3\ 4\ 5)$

then $P_\sigma^{-1}=(5\,4\,3\,2\,1)=(1\,5\,4\,3\,2)$. The action of P_σ on an ordered set of numbers Z and the subsequent action of P_σ^{-1} on the result reproduces Z.

$$P_\sigma^{-1}\times P_\sigma Z = P_\sigma \times P_\sigma^{-1} Z = Z \tag{16}$$

The interconversion $\mathbf{M}_\sigma \rightleftharpoons \mathbf{M}_{\sigma'}$ of two permutational isomers $\mathbf{M}_\sigma$ and $\mathbf{M}_{\sigma'}$ is described by the permutation operators $I_{\sigma\sigma'}$ and $I_{\sigma'\sigma}=I_{\sigma\sigma'}^{-1}$ which we call the *isomerizers*. They are derived from P_σ and $P_{\sigma'}$ as shown in eq. (1), (1a) and (17).

$$\binom{1}{s}_\sigma = \binom{P_{\sigma'}\,n}{n} \tag{1a}$$

By solving eq. (1) for $\binom{1}{s}_0$ and combining with eq. (1a) one gets eq. (17):

$$\binom{1}{s}_{\sigma'} = \binom{P_\sigma\, P_\sigma^{-1}\, P_\sigma n}{n} = \binom{I_{\sigma\sigma}\, P_\sigma n}{n} \tag{17}$$

Therefore:

$$I_{\sigma\sigma'} = P_{\sigma'} P_\sigma^{-1} \tag{17a}$$

and

$$I_{\sigma'\sigma} = P_\sigma P_{\sigma'}^{-1} \tag{17b}$$

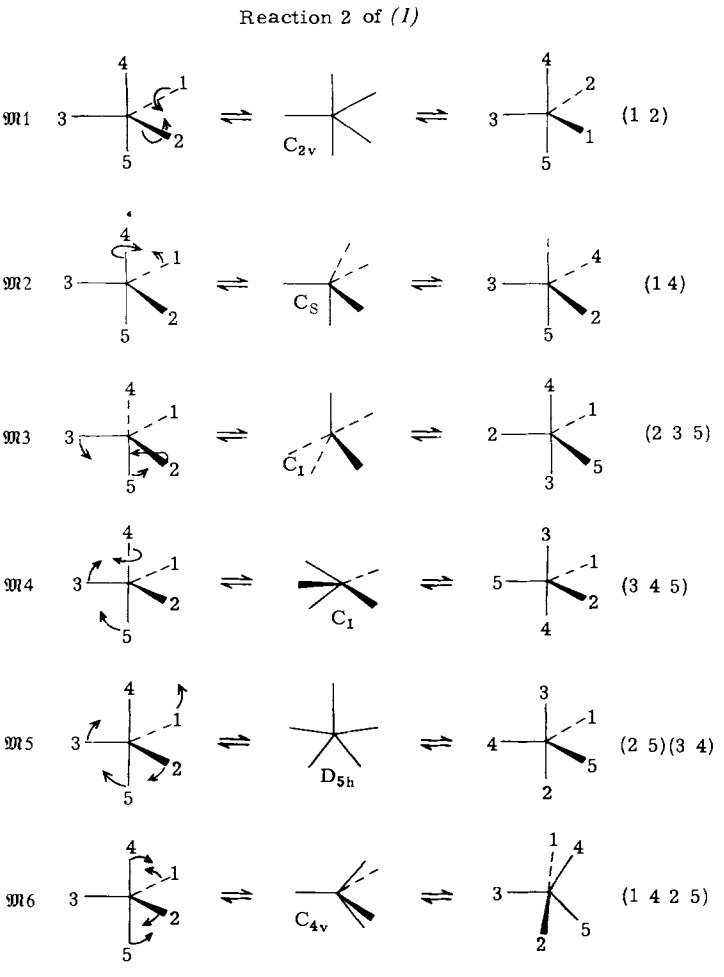
The isomerizers for all molecules of a particular class of permutation isomers with TBP skeletons *(2)* and the ligand set L belong to the symmetric group S_5. Elements of S_5 can be divided into seven classes (of conjugate elements) K_1 — K_5, where $K_1=E$ is the identity operator ("do nothing"):

$$\begin{aligned}
S_5 &= \{K_1,\ldots,K_5\}\\
K_1 &= \{\mathrm{E}\}\\
K_2 &= \{(1\,2),\ (1\,3),\cdots,(4\,5)\}\\
K_3 &= \{(1\,2\,3),\ (1\,2\,4),\ldots,(3\,5\,4)\}\\
K_{2+2} &= \{(1\,2)(3\,4),\ (1\,2)(3\,5),\ldots,(2\,5)(3\,4)\}\\
K_4 &= \{(1\,2\,3\,4),\ (1\,2\,3\,5),\ldots,(2\,5\,4\,3)\}\\
K_{2+3} &= \{(1\,2)(3\,4\,5),\ (1\,3)(2\,4\,5),\ldots,(4\,5)(2\,4\,3)\}\\
K_5 &= \{(1\,2\,3\,4\,5),\ (1\,3\,2\,4\,5),\ldots,(1\,5\,4\,3\,2)\}
\end{aligned} \tag{18}$$

5.2. Mechanistic Alternatives

From eq. (8) it follows that the classes of the group S_5 correspond to the conceivable types of isomerization mechanisms of a class of isomers with a TBP skeleton and the ligand set L. If these permutations represent regular reorganization processes of pentacoordinate molecules with five different ligands on an asymmetric skeleton, each permutation relates to a different process and the classes K_2—K_5 represent types of mechanisms. However, if the pentacoordinate skeleton has some symmetry, *e.g.* a TBP skeleton with D_{3h} symmetry, or some of the ligands are equivalent, then some of the mechanisms of a class $K_x \subset S_5$ have common features and form a subclass[67] within K_x which collectively can be considered a "mechanism".

Muetterties[32] has recently published some conceivable mechanisms, $\mathfrak{M}1$—$\mathfrak{M}6$, for the rearrangement of TBP molecules by regular processes. Skeletal symmetries of the hypothetical barrier situations were included and are shown below with the proper mechanism:

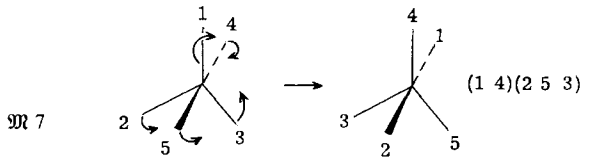


Mechanisms $\mathfrak{M}1$—$\mathfrak{M}6$ are assigned to the classes of the symmetric group S_5 as follows: $\mathfrak{M}1$ and $\mathfrak{M}2$ belong to subclasses of K_2, $\mathfrak{M}3$ and $\mathfrak{M}4$ belong to subclasses of K_3, $\mathfrak{M}5$ belongs to K_{2+2}, and $\mathfrak{M}6$ is represented by the alternating permutations K_{4a} of the class K_4.

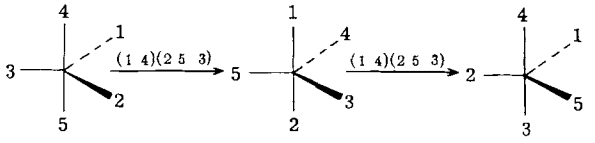
$\mathfrak{M}6$ describes the so-called *Berry pseudorotation mechanism*[3] (BPR). The subclass K_{4a} contains only cyclic permutations of four elements where the indices of the apical and equatorial ligands alternate. The cycle does not act on the pivot. K_{4a} is a proper subclass as its elements are mutually conjugate.

The process illustrated by *(1)* → *(3b)* (Reaction 1b; see also Reaction 3, $\mathfrak{M}7$ and Reaction 7 A_1—A_4) is not only a conceivable but also a physically probable alternate possibility as a regular process (see Section 4.1) for the rearrangement of TBP molecules. We choose the name "*Turnstile Rotation*" TR[2,4] to describe this mechanism. That it was not considered by *Muetterties* may be due to the fact that in graphic representation it cannot immediately be recognized as differing from $\mathfrak{M}2$ and $\mathfrak{M}3$ which have 180° and 120° barriers respectively whereas $\mathfrak{M}7$ has a 60° barrier.

Reaction 3 of *(1)*



$(TR)^2 = [(1\ 4)(2\ 5\ 3)]^2$



The TR process is described by permutations of a subclass of the class $\boldsymbol{K}_{2+3}$ in which one apical and one equatorial ligand belong to the cycle of two elements and the remaining ligands belong to the cycle of three. By inspection, one sees immediately that two successive TR processes with the same pair-trio, $(TR)^2$, correspond to the result of mechanism 𝔐3 of *Muetterties*, *e.g.* $[(1\,4)(2\,5\,3)]\,[(1\,4)(2\,5\,3)] = (2\,5\,3)$.

An analogous threefold process, $(TR)^3$, *e.g.* $[(1\,4)(2\,5\,3)]^3 = (1\,4)$, leads to the result from mechanism 𝔐2.

Since molecules are not restricted to any certain spatial arrangement, the internal rotation of some moiety of a molecule relative to the rest of the molecule can only be described in terms of a relative internal rotation. Therefore, the "ditopal" and "tritopal" rotations of some part of a molecule cannot be treated separately—as in the mechanisms 𝔐2 and 𝔐3—but in fact, correspond to double and triple TR processes.

Mechanisms 𝔐6 (BPR) and 𝔐7 (TR) yield equivalent results but differ fundamentally in their motions and formal representations.

5.3. BPR Mechanism

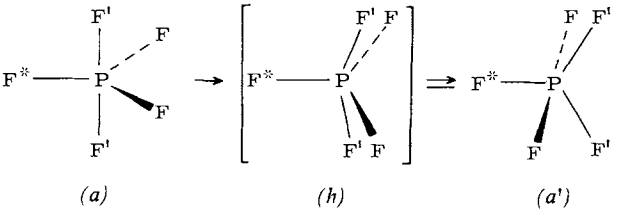
Electron diffraction data[19] of PF_5 *(8)* and analogous phosphoranes as well as IR, Raman spectra[33], and nuclear quadrupole resonance data[34] show that these compounds exist as trigonal bipyramidal compounds in which the apical bond distances are slightly longer than equatorial ones; as expected, the F—P distances are different (see Section 3.2).

However, at temperatures above -100 °C NMR data reveal that for *(8)* there is one fluorine resonance. This equivalency for all fluorine atoms indicates that rapid positional exchange is taking place[3, 35].

Berry[36] assumed that each of two apical and equatorial fluorines were exchanged pairwise by synchronous bending motions while the third equatorial fluorine, the "pivot", does not participate in the motion, but remains in its original skeletal position (marked as the pivot F* in reaction 4).

Here, the F-ligands, originally equatorial, move within plane A (see Fig. 1) from their original position towards the pivot F* (∢ FPF: 120° → 180°) and assume the "new" apical positions. Simultaneously, the ligands F', originally apical, move in plane B away from the pivot F* (∢ F'PF': 180° → 120°) into their "new" equatorial positions. Both pairwise motions occur in a synchronous, concerted fashion. During these flexional motions the bond distances adjust to the new TBP skeletal arrangement. In the idealized cases, the molecule passes through a barrier situation (transition state) with C_{4v} symmetry. After the BPR process the PF_5 molecule is oriented as if the entire molecule had rotated by 90° about the pivotal bond (see Reaction 4), although neither an internal rotation nor a rotation of the whole molecule has taken place; hence the original name, "pseudorotation"[36]. Of all the mechanisms 𝔐1—𝔐7, only the BPR process 𝔐6 occurs without any relative rotation of parts of the molecule with respect to each other. That this is so is immediately obvious upon inspection of Fig. 1, noting that the ligands travel in the A and B planes without internal rotation.

Reaction 4 of *(8)*



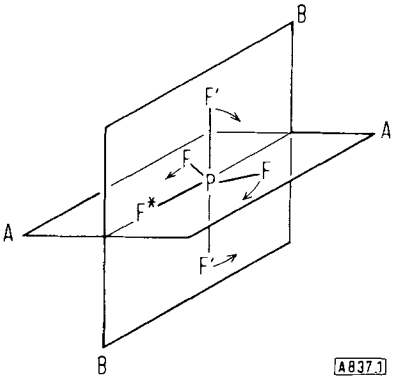


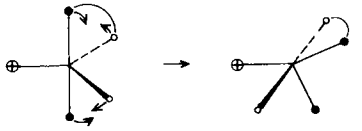
Fig. 1. Components of motion for BPR.

By internal rotation we mean the rotation of a ligand subset of two or three ligands *vs.* the rest of the molecule with synchronous deformation of the bonds at the central atom which, in contrast to the interconversions of rotamers, is a concerted flexion of the TBP skeleton. To determine whether or not a motion contains an internal rotation, it is necessary to analyze the whole process. Motions occurring without angular momentum, such as the flexions described in Fig. 1, are not considered *internal rotations*. As soon as two or more ligands participate in cyclic structures the situation differs fundamentally from the case of acyclic structures, a fact not brought out previously. The following example may illustrate the latter statement. A cyclic TBP molecule *(21)* undergoes a rearrangement by BPR as shown in reaction 5.

Participation of the ligand pair which belongs to the ring corresponds to a rotation of all the ring nuclei and not only

those bonded to the central atom; this rotation is an essential part of the motion.

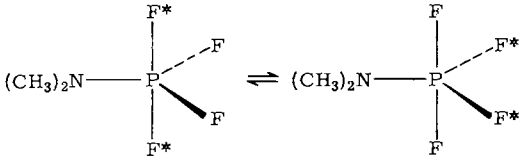
Reaction 5 of *(21)*



(a) *(b)*

Whitesides and *Mitchell*[38] contributed to the understanding of pentatopal rearrangements in a fundamental manner. They analyzed the temperature dependent ^{19}F-NMR spectrum of *(22)*.

Reaction 6 of *(22)*



(a) *(b)*

At low temperatures ($T \leq -100$ °C) the structure of *(22a)* is frozen, *i.e.* the dimethylamino group and two of the F atoms occupy the equatorial positions and the other two F*, the apical sites. As determined by NMR line shape analysis in the temperature range -100 °C to -50 °C, the apical and equatorial fluorines F* and F exchange their positions in a pairwise, concerted fashion. F and F* do not mix and are distinguishable in the ^{19}F-NMR spectrum as "inseparable couples". From this it may be concluded that none of the previously published "non-Berry" alternatives $\mathfrak{M}$ 1 — $\mathfrak{M}$ 5 of the BPR can be responsible for the positional exchange noted in *(22)*.

On the basis of the BPR mechanism, reaction 6 is interpreted as follows: in agreement with the polarity rule[20, 27, 28] (see also Table 1 and Section 3.3.1) the dimethylamino group of *(22)* with its relatively lower electronegativity tends not to occupy apical positions and thus must serve as the pivot.

5.4. Calculated BPR Model Situations

A choice between two mechanistic alternatives based solely on the results of quantum mechanical calculations would be overtaxing the predictive power of these procedures. Nevertheless, it is interesting to examine the assumed pathways with regard to their energy barriers to rearrangement.

Although the absolute values of the energies calculated for this study contain some uncertainty, comparison of binding energy trends in model species for both mechanisms is realistic. The fact that the calculated energy barriers of BPR and TR are reasonably low and both lie within the 5—10 kcal/mol range of the energy barrier observed for the isomerization of PF_5 indicates that neither mechanism can be excluded for quantum mechanical reasons. Furthermore, the calculated BE data for the essential species of the investigated processes contribute to certain ideas concerning the reaction coordinate diagrams for these mechanisms.

The absolute and relative BE data listed in Table 13 for PF_5 molecules which have undergone some deformation illustrate the BPR process. The calculations were accomplished with the aid of an IBM 360/65 computer using the CNDO/2 calculation method (see Section 3.2). Within the limitations of the latter, the following may be concluded from Table 13:

The BPR of *(8a)* and *(8a')* (see also Fig. 2) proceed by synchronous movement of the apical and equatorial ligand pairs *via* species approximated by *(8g)*, *(8h)*, and *(8g')*.

Table 13. BE data for the BPR model situation of *(8)*.

(8)	F—P—F	Angle deformation (°)	Abs. BE (kcal/mol)	Rel. BE (kcal/mol)
(b)	e-e	120 → 90	−596.0	10.1
(c)	e-e	120 → 105	−603.9	2.2
(d)	e-e	120 → 135	−604.3	1.8
(e)	e-e	120 → 180	−579.9	27.2
(f)	a-a	180 → 165	−602.1	4.0
(g)	e-e a-a	120 → 135 180 → 165	−604.1	2.0
(h)	e-e a-a	120 → 150 180 → 150	−602.6	3.5

The rather high value for the BE of *(8e)* suggests that BPR does not occur by a stepwise mechanism, first deforming the diequatorial FPF angle to 180° and then moving the originally apical ligands into their new diequatorial sites. Apical bonds of *(8a)* are "stiffer" than the equatorial.

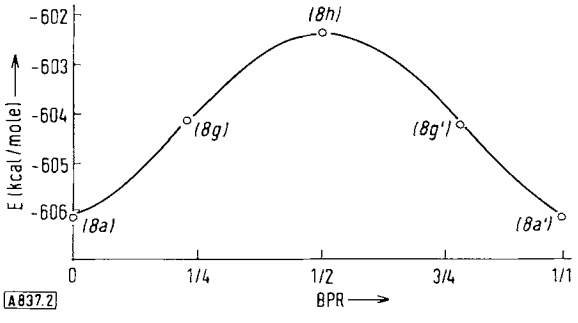
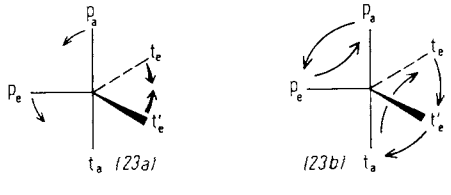


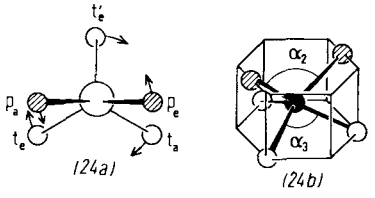
Fig. 2. Calculated reaction coordinate diagram of BPR for PF_5.

5.5. The TR Mechanism

$\mathfrak{M}$ 7, the TR mechanism, is the only alternative to BPR which is consistent with the results of the Whitesides-Mitchell experiment[38] and all other known observations. The TR mechanism is characterized by its unique motion and is illustrated by the models *(23a)* and *(23b)*.



A displacement of two equatorial ligands (t_e and t'_e in *(23a)*) reducing the original 120° angle to ≈90° combined with the simultaneous bending of the apical and equatorial ligands (p_a and p_e in *(23a)*) by approximately 9° produces the species *(23b)*. An initial relative internal rotation of the ligand pair $p_a + p_e$ *vs.* the ligand trio $t_a + t_e + t'_e$ idealized in *(23b)* is superimposed upon both the above vibrational motions. The combination of these three motions leads to the barrier situation *(24)* (30°-TR) after a relative internal rotation of $\Delta\varphi = 30°$,

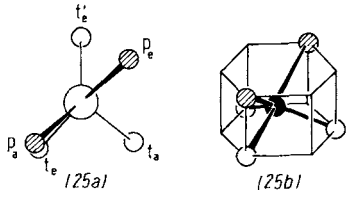


(24a) *(24b)*

and from there by further 30° rotation and restoration of the TBP angles yields the new conformer of the original TBP molecule.

In species *(24)*, the 30°-TR barrier state may be viewed as in *(24a)* where p_a and p_e are above the plane of the page and t_e, t'_e and t_a are below the plane. Alternately, one can use the regular hexagonal prism as a steric reference system to illustrate the same geometry.

Further, *(24)* possesses a skeletal plane of reflection giving it C_s symmetry as well as an approximate local C_{2v} skeletal symmetry for the pair and analogous local C_{3v} symmetry for the trio. Another way of describing the TR process makes use of the fact that it can be viewed approximately as a combination of rotations about local C_2 and C_3 axes with a total internal rotation of $\left.\begin{matrix}60°\\300°\end{matrix}\right\} = 180 \pm 120°$. The "staggered" TR-30° barrier, *(24)*, is halfway between two eclipsed TR model structures *(25)*, the 0° TR, which are reached by ±30° relative rotations of the pair (●) *vs.* the trio (○) of *(24)*.



(25a) *(25b)*

5.6. Calculated TR Model Situations

Table 14 contains BE data for TR barrier models *(24)* of PF_5 again obtained by the use of the CNDO/2 method (see Section 3.2 and 5.4). From Table 14, the lowest energy TR barrier is found at $\alpha_2 \approx 85°$ and $\alpha_3 \approx 95°$. It should be pointed out that, within narrow limits, the BE of *(24)* is not very sensitive towards a variation of α_2 and α_3.

The solid line in Fig. 3 represents a TR process according to *(23a)* and *(23b)* (see *(8b)* and *(8l)*). The transition from *(8l)* to *(8a')* proceeds *via* a "mirror image" of the process *(8a)* → *(8l)*.

Again, it is interesting to note that PF_5 in the geometric situation *(8m)*, whose nuclear skeletal coordinates correspond to the average of two eclipsed 0°-TR species, is energetically quite favorable, meaning that some energetically *allowed* pathways are available by which a *switch of ligands* from a pair to a trio or *vice versa* can occur in a TR species, thereby forming new pair-trio combinations.

Table 14. Calculated BE-data (kcal/mol) of PF_5 in the staggered 30°-TR barrier model situation *(24)* as a function of the pair and trio angles α_2 and α_3.

α_3 \ α_2	80°	85°	90°	95°
85°		−591.4	−591.3	−589.5
90°	−594.0	−595.5	−595.0	−592.5
95°	−596.0	−597.0	−595.9	−592.8
100°		−594.4	−592.3	−588.1

The potential surface for the isomerization of PF_5 does not contain high barriers between the BPR barrier model

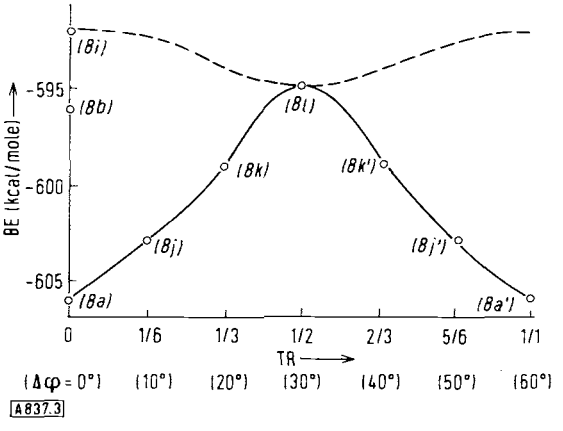


Fig. 3. Reaction diagram for a TR model process of PF_5 with $\alpha_2 = \alpha_3 = 90°$.

(8h) and the staggered 30°-TR model *(8l)*. While these differences arise due to differences in symmetry, they are small enough for interconversions of these species to seem conceivable.

The present BE data show that there are rather wide areas of the potential surface available for the TR barrier situation which may possibly include the BPR barrier geometry as a special case. Hence, the TR process can proceed *via* a "wide pass" on the potential surface, an entropy favored condition, whereas the BPR process, as defined with a C_{4v} barrier situation, is confined to a considerably smaller region of the potential surface at the saddle point.

An investigation of the valence electron distribution in the TR and BPR barrier models of PF_5 does not reveal dramatic differences: electron charge on the central P atom varies by 0.06%; the P 3d contributions to the stability of the species are essentially equal. Deviations of electron density on individual F atoms from the mean value of the ligand set is *ca.* 10% larger in the BPR barrier model. The

latter's pivot ligand bears less electron density than the other four ligands which leads to the conclusion *cum grano salis* that among the conceivable BPR processes, one is preferred whose pivot is the least electronegative of the ligand set, *i.e.* the ligand whose electron density loss yields

A BPR of *(26)* with e as a pivot (Reaction 7A) leads to *(26a)* and is described by the cyclic permutation (a e'' a' e'). The same result *(26)* $\rightleftharpoons$ *(26a)* is achieved by any of the four TR processes (reactions $7A_1$—$7A_4$), represented by one each of the permutations (e e'' a) (a' e'), (e e'' a') (a e'),

Table 15. Calculated BE data of model situations which PF_5 conceivably passes during TR processes.

(8)	Polar coordinate angles subtended by the F-atoms ($r_{PF} \approx 1.73$ Å) φ_1 θ_1	φ_2 θ_2	φ_3 θ_3	φ_4 θ_4	φ_5 θ_5	BE (kcal/mol)
(a), TBP	71° 34′ 114° 06′	−71° 34′ 114° 06′	180° 35° 16′	0° 54° 44′	180° 125° 16′	−606.1
(i), 0°-TR	60° 125° 16′	−60° 125° 16′	180° 45°	0° 45°	180° 125° 16′	−592.0
(j), 10°-TR	57° 43′ 117° 49′	−77° 42′ 117° 49′	180° 38° 31′	0° 57° 29′	170° 125° 16′	−603.5
(k), 20°-TR	43° 51′ 121° 33′	−83° 51′ 121° 33′	180° 41° 45′	0° 48° 15′	160° 125° 16′	−599.1
(l), 30°-TR	30° 125° 16′	−90° 125° 16′	180° 45°	0° 45°	150° 125° 16′	−595.0
(m), "0°–0°-switch" Type I	45° 94° 52′	−67° 30′ 90°	180° 85° 08′	−135° 4° 52′	180° 175° 08′	−600.3

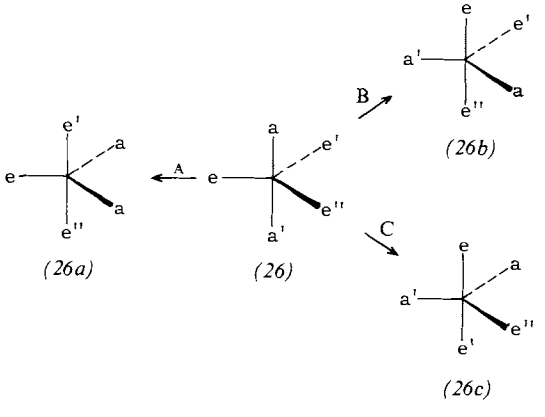
the smallest increase in energy (see Section 2.2). Calculated results also demonstrate that the BE of TR barrier models are less affected by small changes in bond length and angles than the BE of the analogous BPR model. This may be due, in part, to the higher symmetry of the latter, for symmetry is the favorite *panacea* for many obscure relationships. We suspect that for pentacoordinate P compounds, effects mentioned in Section 3.3.2 will contribute to the preference of the BPR mechanism in compounds of the general formula PXY_4 but favor the TR process in compounds of the type PX_2Y_3.

5.7. Common Features and Differences of BPR and TR

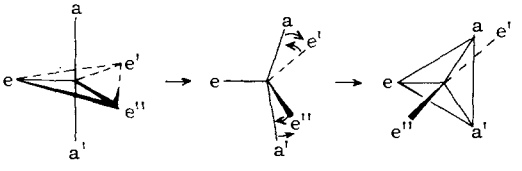
5.7.1. Equivalent Results of BPR and TR

According to reaction 7—$7A_4$ there are four equivalent TR processes for each BPR process. One would expect, therefore, that the TR process has a higher probability than the equivalent BPR process (see Section 5.6).

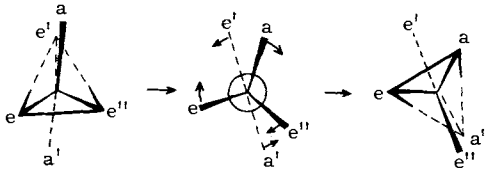
Reaction 7 of *(26)*



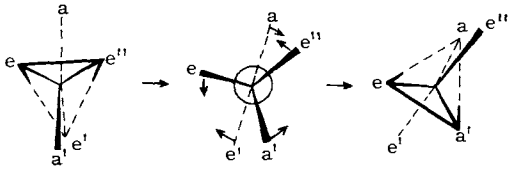
Reaction 7A (a e'' a' e')



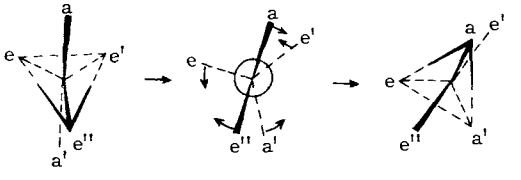
Reaction $7A_1$ (e e'' a)(a' e')



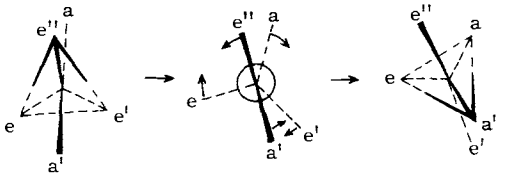
Reaction $7A_2$ (e e'' a')(a e')



Reaction $7A_3$ (e e' a')(a e'')



Reaction $7A_4$ (e e' a)(a' e'')



(e e' a) (a e''), and (e e' a) (a' e''). Similarly, *(26)* can be transformed into *(26b)* or *(26c)* by BPR processes to which there are also four equivalent TR processes. The latter are characterized by the fact that they always contain the pivot of the corresponding BPR in the "trio" which then undergoes relative rotation such that the pivot replaces the other originally equatorial ligand of the trio.

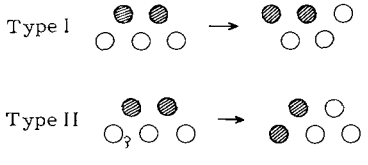
If one combines the BPR process of reaction 7A with suitably chosen rotations of the whole molecule, the resulting isomer is identical to the results of reactions $7A_1$—$7A_4$, although the mechanism differs substantially.

While both BPR and TR processes yield the same product, many differences exist between them. Particularly important among these is the fact that the BPR *does not contain any relative internal rotation* about an axis passing through the central atom while the TR process *is an internal rotation.* Resulting motions for both mechanisms differ geometrically relative to their local symmetries operating on a potential surface of different shape (see Section 5.7.3.2).

Both mechanisms, among the alternatives $\mathfrak{M}1$—$\mathfrak{M}7$ available (Section 5.2), can proceed with conservation of angular momentum intramolecularly in the idealized case. BPR accomplishes this since no rotation is involved, while the TR proceeds such that the pair and trio rotate in opposite directions with equal angular momentum but of opposite algebraic sign.

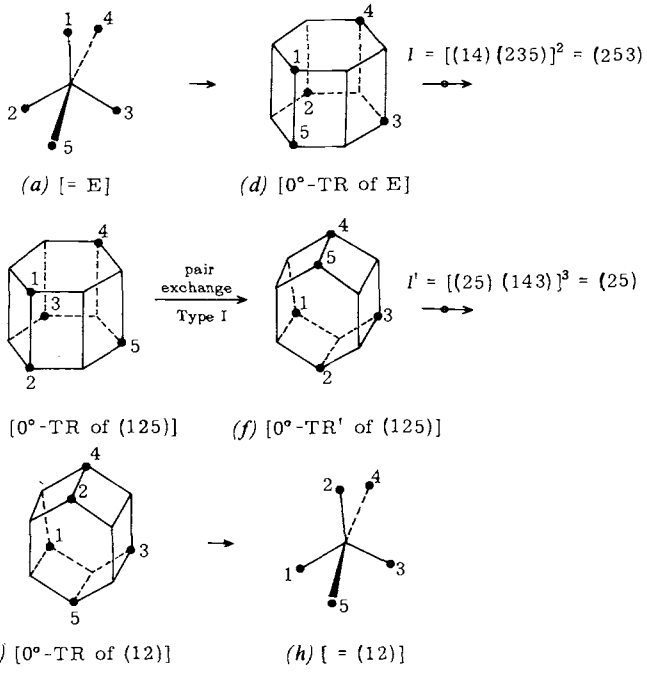
Interconversions of TBP molecules occur by a single BPR or TR step while in other instances several processes are required (see graphs 1—4). The analysis of such sequences reveals a further important difference between the two processes. A repetition of a BPR with the same pivot leads back to the original permutation isomer, $(BPR)^2 = E$, whereas it requires a six-fold TR with the same pair-trio combination to restore the original isomer, $(TR)^6 = E$. It must be pointed out, however, that the $(TR)^2$ may lead to E if the rotational direction of the second TR opposes the first. While it seems reasonable to assume that angular momentum would carry the trio in the same direction, the fact still remains that the direction can reverse in the process. However, the BPR *must* change pivots after each process if more than a single isomer is to be achieved. With TR, "productive" sequences of single steps can be accomplished with the same pair-trio unit.

A sequence of TR with a constant pair-trio combination can proceed step by step, (with a single TR process between two TBP molecules) but it is also conceivable that the result of repeated TR without crossovers (change of pair-trios in a TBP intermediate) is achieved *via* 0°-TR situations bypassing the intermediate TBP. One can envision changes of pair-trio combinations on the barrier level as a "switch" where the pair-trio change occurs between various 0°-TR or 30°-TR situations (*e.g.* (0°-TR)—(0°-TR)',...(30°-TR) to (30°-TR)').



In reaction 8 we employ models to illustrate a conceivable, one step pathway for the inversion of TBP molecules with a 0°—0° switch of type I in which ligand 3 of the trio in *(1e)* combines with the 1—4 pair and forms the trio 1—4—3 of *(1f)*.

Reaction 8 of *(1)*



(a) [= E] *(d)* [0°-TR of E]

(e) [0°-TR of (125)] *(f)* [0°-TR' of (125)]

(g) [0°-TR of (12)] *(h)* [= (12)]

If the barriers for all conceivable switches are sufficiently low, all ligands of a pentacoordinate molecule become directly permutable. Thus the full dynamic symmetry of the TBP skeleton is attained in one step.

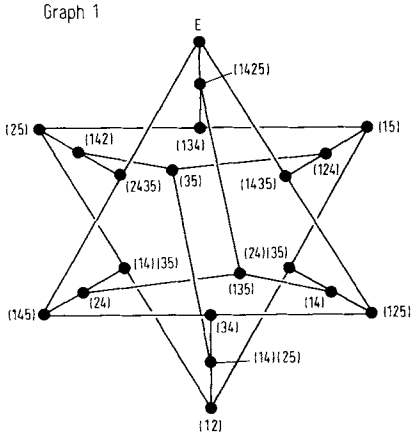
5.7.2. Sequences of BPR and TR Processes and Their Graphs

As the TR process yields products equivalent to those of the BPR the graphs[5d, 14, 15, 39, 40] originally developed for BPR processes also hold for TR (see Graphs 1—16 and, for comparison with the graphs of other authors, see Table 1).

Graph 1: The points correspond to the permutation isomers (with skeleton *(2)* and five different ligands) that are given by their descriptors[11] (see Table 1). Connecting lines are the BPR or TR processes respectively. Pairs of opposing points which are at inversion symmetry locations correspond to pairs of antipodes, *e.g.* E and (1 2). This graph is derived from the one originally proposed by *Ramirez* and *Lauterbur*[14]. As a consequence of the algebraic properties of the isomerizer[1], those permutation isomers in graph 1 connected to E with a single line have descriptors of the class $\boldsymbol{K}_{4a}$ (see Sections 5.1 and 5.2). Those permutation isomers obtained from $\mathbf{M}_0$ ($\equiv$E) by TR^2 have descriptors belonging to a subclass of $\boldsymbol{K}_3$ (two equatorial symbols, one apical; with the seeming exception (1 4 5) = (1 5 2)) or $\boldsymbol{K}_2$ (one equatorial, one apical symbol), respectively. Isomers with descriptors to the class $\boldsymbol{K}_{2+2}$ are obtained from $\mathbf{M}_0$ by two $(TR)^3$ processes with common elements in the pairs.

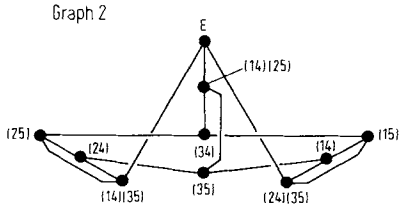
The descriptor (1 2) of the antipode of $\mathbf{M}_0$ belongs to class $\boldsymbol{K}_2$ (with two equatorial or two apical symbols) and corresponds to a five-fold product of TR or BPR isomerizers; in the case of the TR mechanism, at least two of the pairs must be devoid of common elements (see Section 5.7.3).

Graph 1



For the configurational inversion of a TBP molecule with five different ligands, certain sequences of five BPR processes with five different pivots are needed (see Graph 1). Configurational inversion by TR also requires a sequence of five processes but, from the fact that four equivalent TR processes exist for each BPR, it follows that there are $4^5 = 1024$ different TR pathways leading to the same inversion product (see probability factor, Section 5.7.1). Among these pathways there are some with a single crossover after the $(TR)^2$ step (*e.g.* $[(2\ 5)\ (1\ 3\ 4)]^3\ [(1\ 4)\ (2\ 3\ 5)]^2$, see Section 5.2).

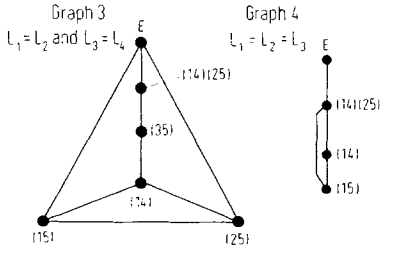
Graph 2



Graph 2: Ligands L_1 and L_2 are equivalent. Achiral molecules are represented in graphs 2 and 3 by points on the mirror line and pairs of antipodes by points which are located symmetrically on either side of the mirror line.

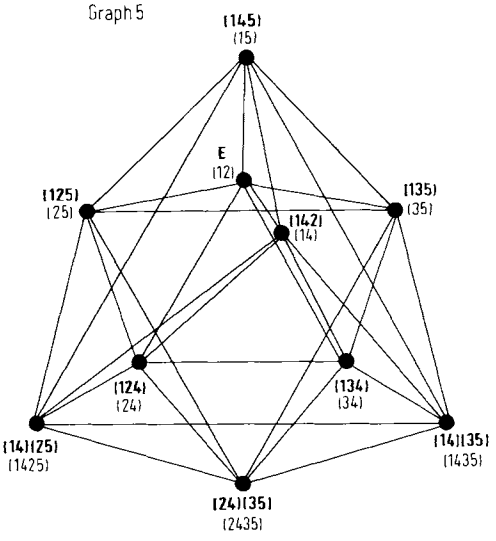
Graph 3
$L_1 = L_2$ and $L_3 = L_4$

Graph 4
$L_1 = L_2 = L_3$



Graph 3: Interconversions of the permutation isomers of *(1)* by TR^2 processes are mapped on this graph (Reaction 2, $\mathfrak{M}$ 3). Permutation isomers of *(1)* belong to two classes denoted by bold face or regular type descriptors. Processes

Graph 5



symbolized by the lines connect only species of the same class, *i.e.* configurational inversion is impossible[5]. If one considers the mutual interconvertibility resulting from $(TR)^2$ processes as an equivalence relation, then the permutation isomers of a class are homochiral (are the conformers of the same classical species, see Section 4.2) and heterochiral to the elements (conformers) of the other class (antipode species).

5.7.3. Summary of the Common Features and Essential Differences of BPR and TR

5.7.3.1. Common Features

1. Both processes are regular rearrangements of TBP pentacoordinate molecules yielding equivalent products.

2. In both processes apical and equatorial ligands are exchanged pairwise in a synchronous, concerted manner.

3. In the ideal case both processes can proceed with conservation of angular momentum.

4. Both processes are energetically allowed.

5.7.3.2. Differences

1. BPR and TR result in differential partitioning of the ligand set (1 + 4 or 2 + 3) respectively, being represented by different subclasses of permutations belonging to the group $\boldsymbol{S}_5$ and being conjugate with regard to the elements of G.

2. For each BPR there are *four* different TR that produce the same result as the BPR. Thus for each sequence of n BPR, there are 4^n equivalent TR sequences.

3. $(BPR)^2 = E$ with constant pivot while $(TR)^6 = E$ with constant pair-trio and trio rotation direction.

4. All ligands participate in a TR process.

5. The TR process is essentially an internal rotation while this is entirely absent from BPR.

6. Motions leading to the barrier species for each process are different (BPR: C_{4v} skeletal symmetry TR: approximate local C_{2v}- and C_{3v}-skeletal symmetries)

7. Ligand motions and energy barriers vary differently as a function of the ligand set and its distribution on the TBP

skeleton; TBP with apical equatorial rings must rearrange by TR.

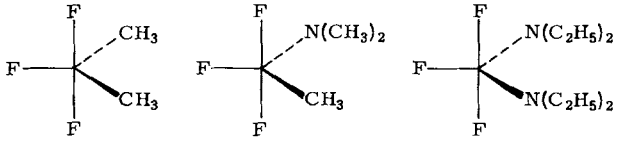
8. Multiple TR sequences can proceed without passing through a TBP intermediate, an ability BPR lacks.

9. TR and their sequences have higher probability than the corresponding sequences of BPR.

6. Discussion of the NMR Spectra from Phosphorane Derivatives and Related Compounds

6.1. Acyclic Systems

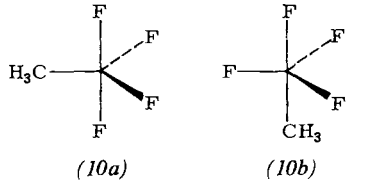
At temperatures below 100°C the ^{19}F-NMR spectra of *(27)*[35], *(28)*[28] and *(29)*[41] indicate two distinguishable fluorines in a ratio of 2:1. It appears then, that no rearrangement of the molecule involving F-exchange between apical and equatorial positions is occurring, either by regular or by irregular processes. Rearrangement by BPR or TR does not take place because any conceivable BPR or TR process produces high energy species having apical methyl or dialkyl amino groups.



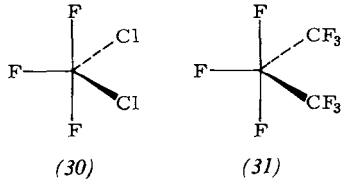
(27) *(28)* *(29)*

From CNDO/2 calculations, we see that *(10b)* (Table 2) is 39 kcal/mol more stable than *(10a)*. Fluorine exchange by $(TR)^2$ does not take place in *(27)*—*(29)* either, probably because 0°-TR species with unreasonable energies would be involved (see Section 5.6 and Table 15).

At temperatures above 25°C, *(30)*[35] and *(31)*[35] (as well as *(8)*, *(10)*, and *(22)*)



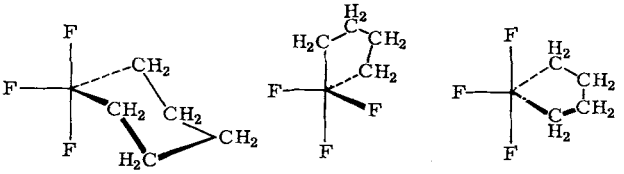
(10a) *(10b)*



(30) *(31)*

exhibit an ^{19}F-NMR signal owing to rapid positional exchange among the fluorines. One can assume that F-exchange proceeds *via* a regular process, for in *(27)*—*(29)* no irregular exchange is observed. Both the BPR and TR are possible for the rearrangement of *(30)* and *(31)*.

In *(10)* and *(22)* the F-exchange operates such that high energy TBP species with an apical methyl or dimethylamino group are avoided, *i.e.*, in the case of BPR the latter groups are pivots and with TR mechanisms, only those processes are allowed in which the pair consists of an apica and equatorial fluorine and the trio rotates such that the organic group proceeds from one equatorial position to another. This is in keeping with the Whitesides-Mitchell experiment (see Section 5.3).



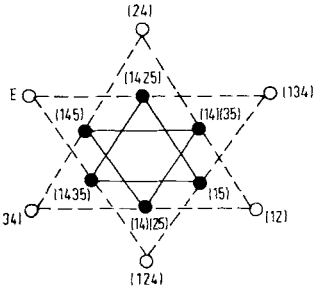
(32) *(33a)* *(33b)*

6.2. Cyclic Systems

The cyclic phosphorane derivatives *(32)*[35] and *(33)*[35] differ fundamentally with respect to their TBP stability. In *(32)* the 6-membered ring preferentially exists in the diequatorial position as predicted by the polarity rule; ring strain[9] is not significant in this position. However, *(33)* is in violation of the polarity rule with the apical-equatorial placement of the ring. Enlargement of an endocyclic bond angle or the compression of an endocyclic C—P—C angle to 108° or less leads to high strain energy while the envelope of the 5-membered ring can accommodate a 90° C—P—C angle with almost no strain (see Table 2, *(18)*). An experimental observation that *(33)*, contrary to *(32)*, undergoes F-exchange is in accord with the above argument. BPR rearrangement of *(33)* with F as a pivot or a TR mechanism with the ring as the pair does not require any high energy species for this process. Such is not the case for *(32)*.

NMR studies of *(34)*[42] indicate that although some permutational isomerization has taken place, there is no configuration inversion of the TBP phosphorane, *i.e.* there is no interconversion of molecules of the classes *(34)* **A** and

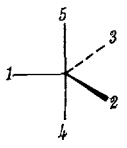
Graph 6



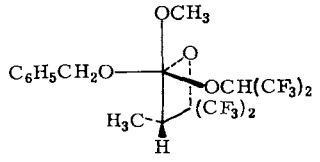
(34) **B**. The isomers E, (1 2 4) and (1 3 4) of the class *(34)* **A** and their epimers (1 2), (2 4) and (3 4) of the class *(34)* **B** carry apical P—C bonds, thus being energetically disfavored. Interpretation of the observations by a $(TR)^2$ mechanism, given in Graph 6, permits the omission of high energy permutation isomers.

In the graphs 6—16, the energetically favorable molecules are symbolized by and the disfavored ones (*e.g.* oxy-

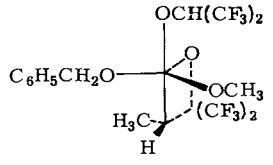
phosphorane derivatives with apical P—C bonds or diequatorial 5-membered rings, see Table 2, *(16)—(18)*) by O. Solid lines correspond to $(TR)^2$ processes (as well as the equivalent BPR) and the broken lines to the TR processes; $(TR)^3$ processes are denoted by an alternating dash-dot line. At first sight, it seems an advantage to write the formulas of the phosphorane derivatives *(1)* with the TBP skeleton and the sequentially numbered set $L_1,\ldots,L_5$ in such a manner that the ligand set is placed upon the skeleton *(2)* in its standard orientation, according to the instructions given for descriptors[1]. In this way, one finds the formula *(34')* E from the reference isomer *(34)* E of *(34)* (with the sequentially numbered[13] ligand set



(2a)



(34') E



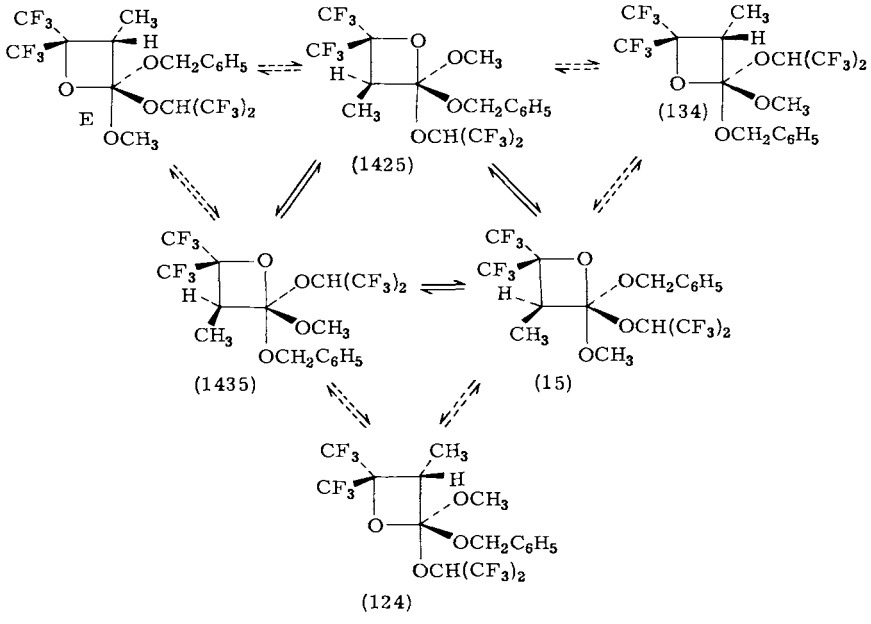
(34') (24)

$L_1 = -O-C(CF_3)_2$ (cyclic)
$L_5 = -CH(CH_3)$

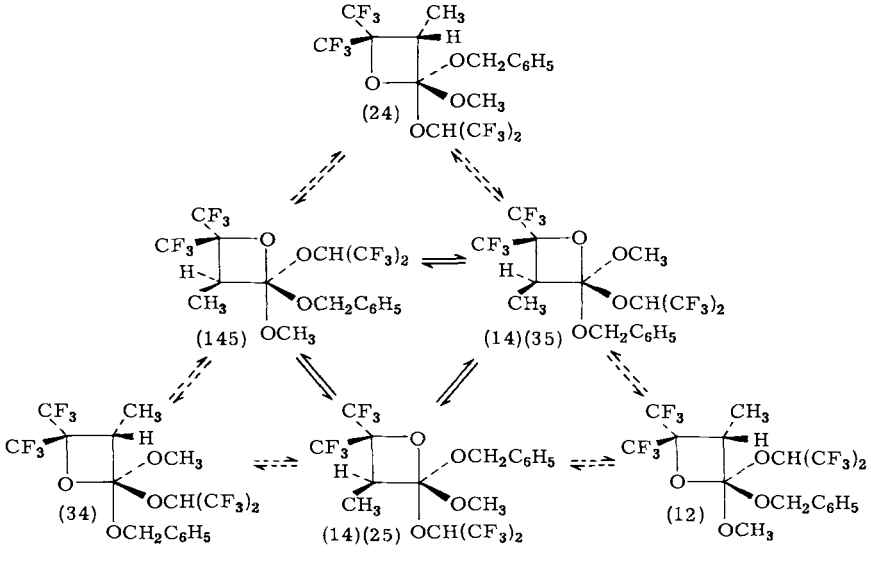
$L_2 = -O-CH(CF_3)_2$
$L_3 = -O-CH_2C_6H_5$
$L_4 = -O-CH_3$

and the skeleton *(2)*) by attaching L_1 to position *1*, L_2 to position *2*, *etc.* and permuting the ligands L_2 and L_4. The following formulas result in graphic difficulty. The more

Reaction 9A of *(34)* **A**



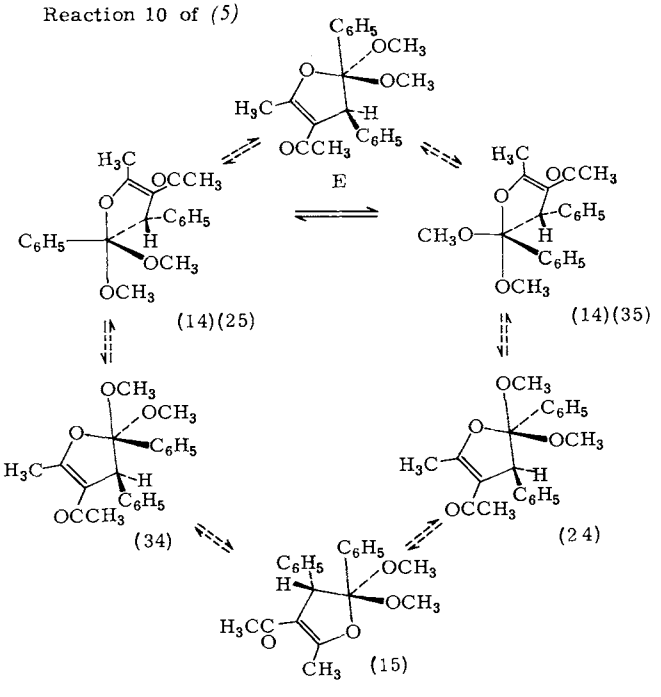
Reaction 9B of *(34)* **B**



readable (and equivalent) formulas *(34)* E and (24) are found by rotating the latter by 180° about the C_2 skeletal axis of symmetry which passes through the central atom and skeletal position *2*. Alternately, one can attach the set of ligands, as described above, to the skeleton *(2a)* which is generated from *(2)* by the permutation (1 3) (4 5) which reduces to a 180° skeletal rotation. For the following examples, the formulas obtained by projecting the descriptor onto a skeleton were not used in each case if they led to graphically awkward representations. Instead, the most readable equivalent formulas were chosen.

Among the following permutation isomers of *(5)*[5a, 6, 43] ($L_2=L_3=OCH_3$, ring L_1+L_5), *(5)* (1 4) is forbidden due to the diapical placement of the 5-membered ring. From the subsequent experimental data (see *(18)*, Table 2, a model for *(5)*) it follows that permutational isomers with a diequatorial 5-membered ring *(5)* (2 5), (3 5) and (2 4) (3 5) occur neither as equilibrating participants in a measurable concentration nor as intermediates of rearrangement processes. The permutation isomers *(5)* (1 5), (2 4) and (3 4) are, as indicated by the polarity rule, further disfavored conformers.

Reaction 10 of *(5)*

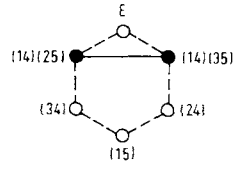


The only stable permutation isomers of *(5)* which occur in observable concentration are *(5)* (1 4) (2 5) and *(5)* (1 4) (3 5).

It can be concluded from the NMR data that at −20° *(5)* exists as a frozen diastereomeric mixture of *(5)* (1 4) (2 5) and *(5)* (1 4) (3 5) in a ratio of about 1:2. (Signals from 4 OCH_3, 2 benzylic protons, 2 CH_3 and 2 ^{31}P are present.) Above 70 °C the interconversion of *(5)* (1 4) (2 5) and *(5)* (1 4) (3 5) is so rapid that it is not observable on the NMR time scale (2 OCH_3, 1 benzylic H, 1 C—CH_3 and 1 ^{31}P); however, the methoxyls do not become equivalent.

The above interconversion takes place as a regular process below 100 °C, since no exchange of C methyl groups is observed. An interpretation of these data by a BPR or the equivalent TR imposes highly unlikely species in the process, either *(5)* E with an apical P—C bond as an intermediate and/or *(5)* (3 4), (1 5) and (2 4) with apical P—C bonds. Since complete exchange of the CH_3O groups has been ruled out by line shape analysis[44], all processes which proceed through an intermediate with a diequatorial ring may be eliminated (see graphs 7 and 1).

Graph 7



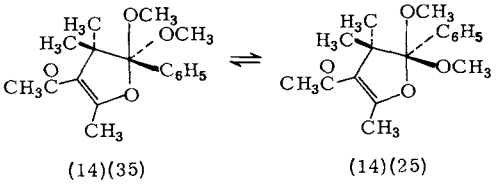
Finally, it should be noted that any conceivable interconversion of *(5)* (1 4) (2 5) and *(5)* (1 4) (3 5) by simple TR or BPR processes must proceed *via (5)* E or *(5)* (1 5) in which the methoxy groups are placed at mirror image skeletal sites (diequatorial or diapical). Both TR pathways (1 4) (2 5)—(3 4)—(1 5)—(2 4)—(1 4) (3 5) and (1 4) (2 5) —E—(1 4) (3 5), which do not proceed *via* intermediates with diequatorial rings, are characterized by the fact that *in each step, the ring can be the pair.* It is a particular advantage for the interpretation of rearrangements of pentacoordinate molecules by a simple or multiple TR mechanism that in the case of systems with four or five membered rings, these and only these must be the pair which seems to be physically reasonable.

Among the possible mechanisms, the double TR with the ring as the pair is the only one which avoids any energetically unreasonable species in order to rationalize the data.

Along with the above example, some of the subsequent cases point out that in the common instance where a pentatopal rearrangement involves a 4—5-membered ring all data can be explained on the basis of a simple or multiple TR in which *the ring is always the pair.*

In analogous systems, *e.g. (35)*[15], without a tetrahedral center of chirality one observes two OCH_3 signals below −8 °C and only one signal above +62 °C. Except for the tetrahedral chiral center the interpretation is similar to the previous case. The pairs of diastereomers of *(5)* correspond to antipode pairs of *(35)*.

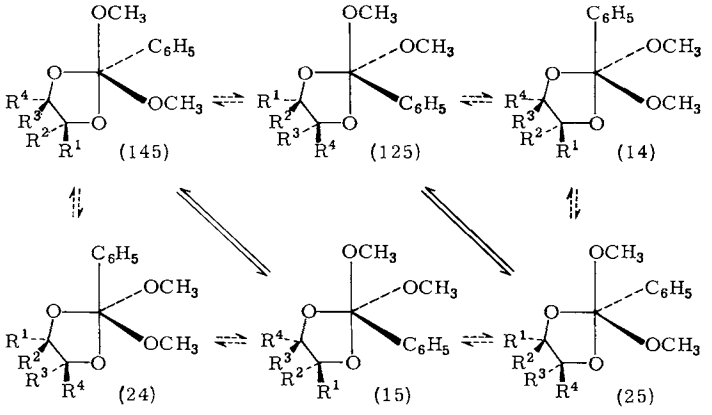
Reaction 11 of *(35)*



At −90 °C to +20 °C for *(36)*—*(38)*[44] ($L_3=L_4=OCH_3$, ring: L_1+L_2), one observes two methoxy group signals in the ^{1}H-NMR spectrum. Reaction 12 is interpreted just like reaction 1 according to Graph 8. In the case of reaction 12, the singular observation that the different apical-equatorial placements of the 5-membered ring are ener-

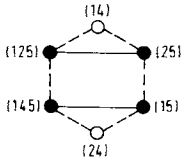
getically similar is the most significant consideration. Here, also, the ring can be the pair in all TR and $(TR)^2$ processes, avoiding all species with a diequatorial ring.

Reaction 12 of *(36)-(38)*



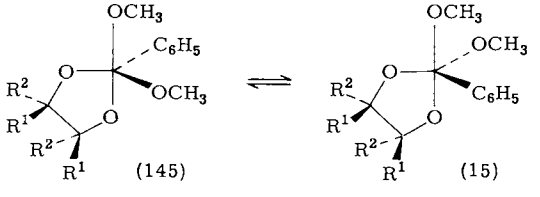
(36): $R^1 = R^2 = CF_3$, $R^3 = COCH_3$, $R^4 = CH_3$
(37): $R^1 = COCH_3$, $R^2 = CH_3$, $R^3 = p\text{-}NO_2\text{-}C_6H_4$, $R^4 = H$
(38): $R^1 = CH_3$, $R^2 = COCH_3$, $R^3 = p\text{-}NO_2\text{-}C_6H_4$, $R^4 = H$

Graph 8



Reaction 13 corresponds to reaction 11 except that the 5-membered ring and its C-bonded set of ligands has a local C_2 axis of symmetry. Consequently, a simple TR, graph 8,

Reaction 13 of *(39)* and *(40)*



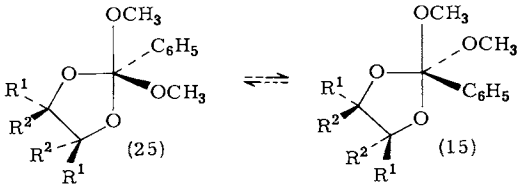
(39): $R^1 = COCH_3$, $R^2 = CH_3$
(40): $R^1 = p\text{-}NO_2\text{-}C_6H_4$, $R^2 = H$

suffices for an inversion of the whole molecule, *i.e.* (1 4 5) =(1 2 5), (1 5)=(2 5). One finds only one OCH_3 signal in the ^{1}H-NMR spectrum above +20 °C[44].

Replacing the local C_2 symmetry of the ring by a local mirror plane symmetry (see Reaction 14) leads to a simplification of graph 8, since the additional equivalence of ligands 1 and 2 in *(41)* and *(42)* means that the permutation isomers (1 2 5) and (1 5) plus (1 4 5) and (2 5) are equivalent (graph 9).

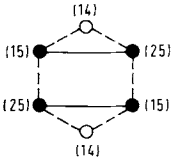
One observes in this case that both the TR and $(TR)^2$ processes yield the same result. However, since the permutation isomers (1 5) and (2 5) are diastereomers and not anti-

Reaction 14 of *(41)* and *(42)*



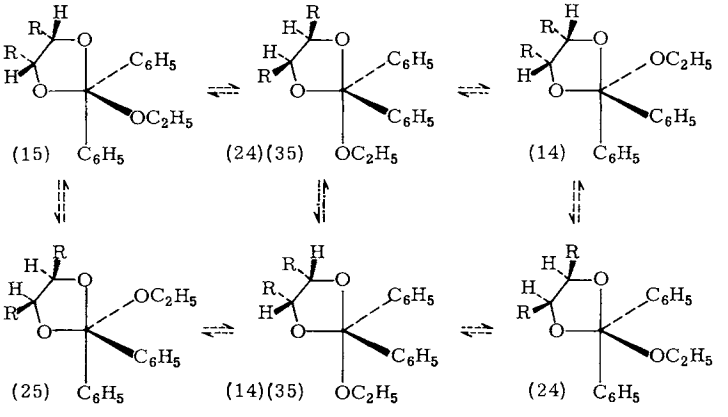
(41): $R^1 = COCH_3$, $R^2 = CH_3$
(42): $R^1 = p\text{-}NO_2\text{-}C_6H_4$, $R^2 = H$

Graph 9

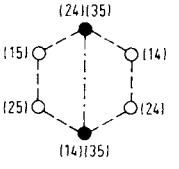


podes, the methoxy groups remain distinguishable; in agreement with this two signals for OCH_3 are found in the ^{1}H-NMR spectrum above +30 °.

Reaction 15 of *(43)*, R = p-NO_2-C_6H_4

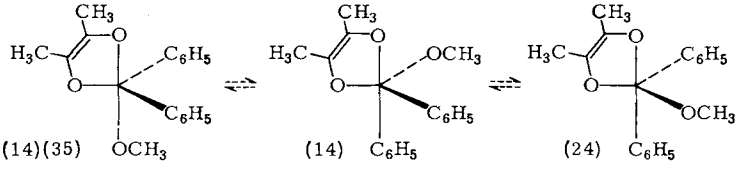


Graph 10

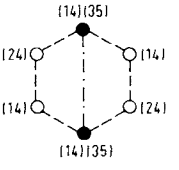


For Reaction 15 ($L_4 = L_5 = C_6H_5$, ring: $L_1 + L_2$) the NMR spectrum shows two benzylic protons at −75 °C, indicat-

Reaction 16 of *(44)*



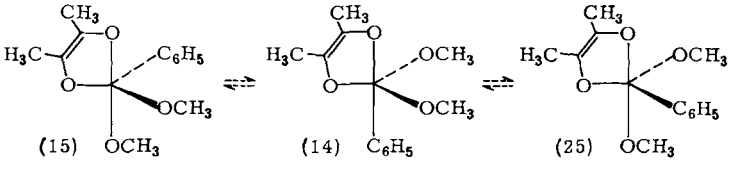
Graph 11



ing a frozen pair of antipodes (1 4) (3 5) and (2 4) (3 5). Antipode invariances are accomplished by an exchange of apical and equatorial benzylic protons; above +30°C only one signal is found for these protons. Here the $(TR)^2$ mechanism with the ring pair is the only process that avoids high energy species in the reaction (see graph 10).

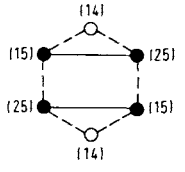
Phosphorane *(44)*[45] produces a ^{1}H-NMR spectrum containing only one C—CH_3 signal between −60° and +160°C. Reaction 16 is interpreted just like reaction 15 but graph 10 can be replaced by the simplified graph 11 since ligands 1 and 2 are equivalent in *(44)*.

Reaction 17 of *(45)*



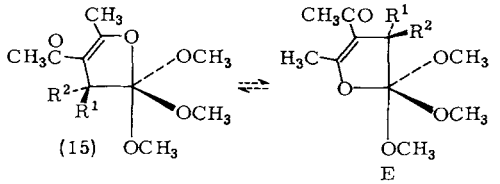
Reaction 17 differs from reaction 16 in that stable permutation isomers of *(45)*[45] ((1 5) and (2 5)) are chiral whereas the stable isomers of *(44)* are achiral species (1 4) (3 5).

Graph 12



The ^{1}H-NMR spectrum reveals one OCH_3 and one C—CH_3 signal in the range −60° to +160°C which indicates the description of the process depicted in graph 12.

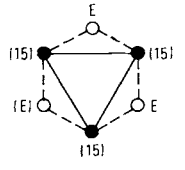
Reaction 18 of *(46)* and *(47)*



(46): $R^1 = C_6H_5$, $R^2 = H$
(47): $R^1 = R^2 = CH_3$

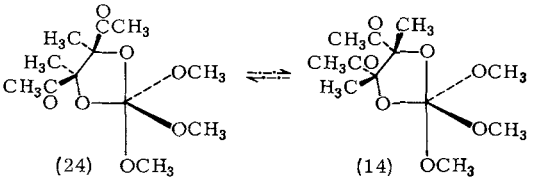
The central atom of TBP molecules with three equivalent ligands cannot be a center of chirality. Consequently, reaction 18 of *(46)* and *(47)* requires only one graph, namely graph 13.

Graph 13

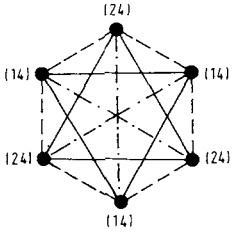


For the frozen structure *(46)* (1 5) three different methoxy peaks exist in the ^{1}H-NMR spectrum at −67°C, and at −28°C only two[15]. Above +25°C or +57°C, respectively, only one methoxy resonance is found.

Reaction 19 of *(48)*



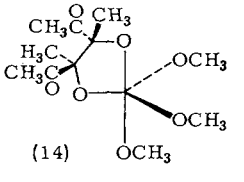
Graph 14



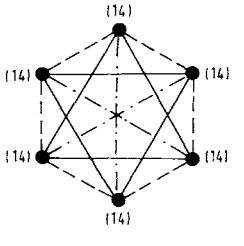
At +30°C, *(48)*[46] ($L_3 = L_4 = L_5 = OCH_3$, ring: $L_1 + L_2$) exhibits one *O*-methyl, one *CO*-methyl, and one *C*-methyl peak in the ^{1}H-NMR spectrum. This can be rationalized by a rearrangement described by graph 14.

A local plane of reflection in the *C*-ligand set of the ring distinguishes *(49)*[46] from *(48)*. For *(49)*, one OCH_3, $COCH_3$ and C—CH_3 is recorded at +30°C. The corresponding graph 15 differs from 14 in that there is only one TBP related descriptor unless one distinguishes between equivalent ligands when assigning the ligand indices.

Reaction 20 of *(49)*



Graph 15

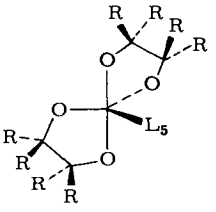


6.3. Spiroidal Systems

Compounds *(50)*[47] and *(51)*—*(54)*[48] possess two types of ^{1}H-NMR spectra as a function of the temperature. In lower temperature ranges two different CH and C—CH_3 signals are recorded, while in a higher range only one signal for each resonance is observed.

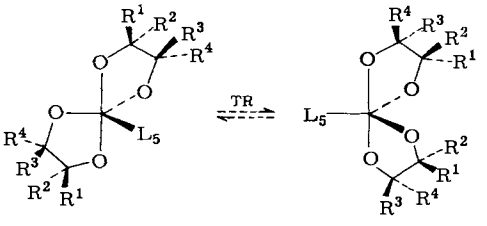
If one retains the original postulate that no 5-membered ring can exist diequatorially, this reaction submits itself

to a TR mechanism for the lower temperature range and a $(TR)^2$ mechanism (with no BPR equivalent) for the upper range indicated in reactions 21a and 21b.

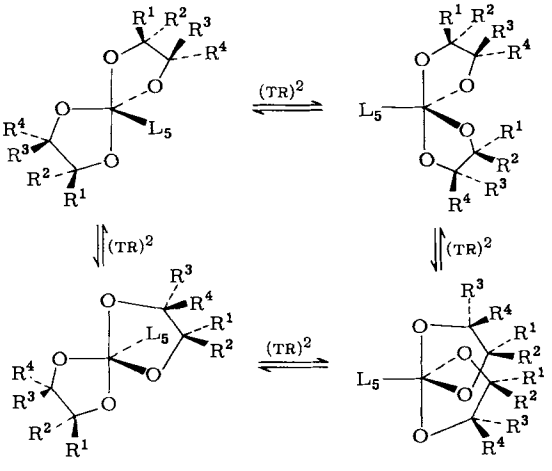


(50): Z = P; R = CH_3; L_5 = H
(51): Z = As; R = H; L_5 = OH
(52): Z = As; R = H; L_5 = OCH_3
(53): Z = As; R = CH_3; L_5 = OH
(54): Z = As; R = CH_3; L_5 = OCH_3
(55): Z = As; R = CH_3; L_5 = C_6H_5

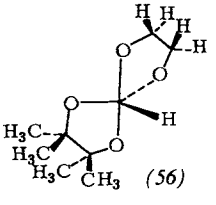
Reaction 21a of *(50)-(55)*



Reaction 21b of *(50)-(54)*



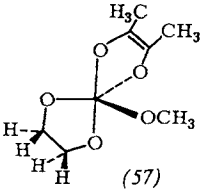
Only one ^{1}H-NMR spectrum is found for *(55)* which corresponds to the low temperature range spectra of *(50)* to *(54)*. From this it follows that the barriers for $(TR)^2$ processes are high for rearrangement in *(55)*. The ^{1}H-NMR spectrum of *(56)*[42] in the range −70 to 0 °C displays two different methyl signals and an AA'BB'X pattern for the methylene protons. Above +37 °C, one resonance is observed for both the methyl groups and the methylene



(56)

protons, the latter exhibiting an A_4X pattern. These data show that in the lower temperature range TR processes dominate when both rings can be the pair. $(TR)^2$ processes predominate in the upper temperature range where both rings must alternate as the pair.

Compound *(57)* contains two substantially different rings, the unsaturated ring being planar while the preferential geometry of the saturated ring is puckered. This deter-

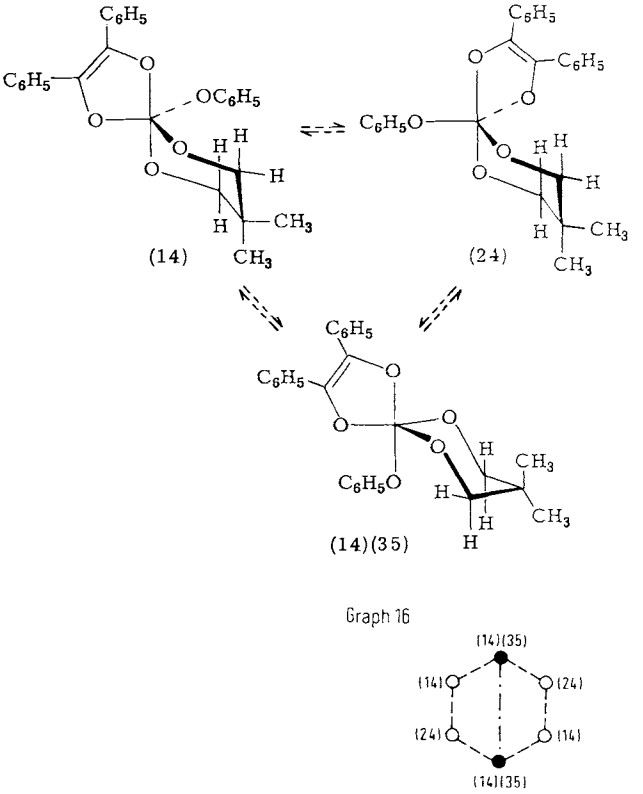


(57)

mines, in part, the strain energy and the magnitude of the O—P—O angle. The ^{1}H-NMR spectrum in the −60 to +110 °C range yields one C—CH_3 signal but a complex pattern from the methylene protons. With the assumption that only the unsaturated ring with the larger O—P—O angle (see Table 2) can function as the pair, TR, $(TR)^2$ and $(TR)^3$ processes yield identical results and thereby are all equally suited for interpretation of the reaction if di-equatorial 5-membered rings are excluded.

Compound *(58)*[49] shows two different C—CH_3 protons and a complex pattern for the methylene protons at +30 °C. By assuming that the 6-membered ring can be apical-equatorial, the data may be rationalized by a single TR process. However, if the 6-membered ring is confined to a diequatorial placement, which is the lowest energy conformation, the $(TR)^3$ is the more likely mechanism.

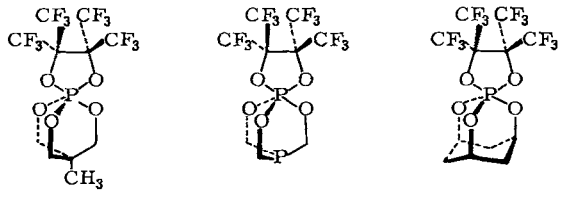
Reaction 22 of *(58)*



Graph 16

6.4. Polycyclic Systems and their Experimentum Crucis

The ^{1}H- and ^{31}P-NMR of *(59)*—*(61)*[1,4,50] were taken over a temperature range of −60 to 0 °C and the ^{19}F-NMR spectrum from −155 to 0 °C.



(59) (60) (61)

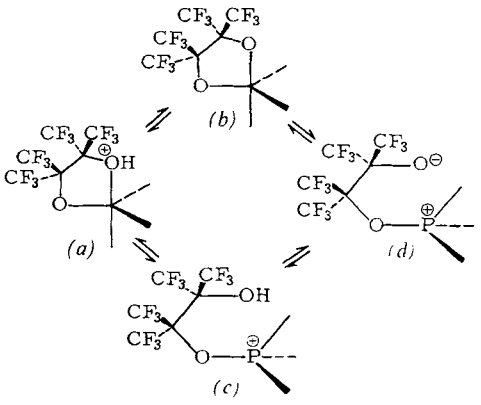
Complete positional exchange is indicated in the ^{1}H-NMR spectrum for all protons with respect to the local C_{3v} symmetries of the bicyclic systems.

Above -80 °C, the ^{19}F-NMR spectrum of *(60)* gives one single resonance, below which broadening occurs. At *ca.* -90 °C coalescence is observed and below -100 °C the signal forms a sharp, complex multiplet corresponding to a frozen structure with a non-planar 5-membered ring. The sharp ^{19}F-NMR doublet of *(61)* broadens at -120 °C, coalesces at -130 °C, and begins to show a single resonance at -140 °C, sharpening at -150 °C. This dramatic difference in the temperature dependence of rearrangement indicates that the barrier to this process is appreciably lower for *(61)* compared to that for *(60)*[*].

On the basis of the TR mechanism, this is precisely what one would expect. The TBP arrangement of the P bond system in *(61)* can only be realized with strain in the adamantanoid moiety of the molecule thereby costing some energy. When deformed into the 30°-TR barrier state where the adamantanoid moiety possesses C_{3v} symmetry, this energy is released, lowering the energy difference between the ground state and the barrier situation. Further, diequatorial 6-membered rings are energetically favored over their apical-equatorial analogs. Thus, a rearrangement process that prevents the latter situation as an intermediate will lower the rearrangement barrier. Less strain exists in the ground state for *(60)*, it may be almost strain free, hence, energy difference between the ground state and the barrier would be greater.

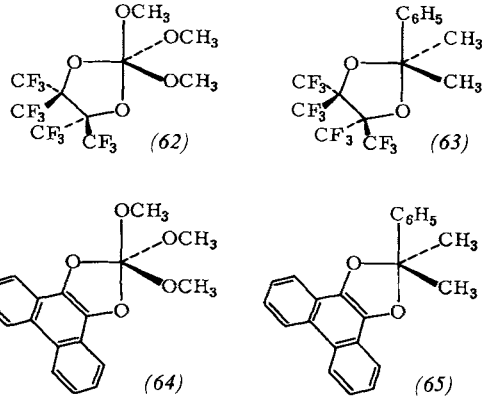
An argument offered against TR rearrangement processes in the examples *(59)—(61)*, holds that the reaction actually proceeds by an irregular process *via* species arising from opening of the 5-membered ring (see Reaction 23). This possibility is ruled out by the data in Table 16, which clearly indicate:

Reaction 23 of *(59)-(61)*



The ^{31}P chemical shift of oxyphosphoranes which undergo rapid equilibria with open chain dipolar structures containing tetracoordinate phosphorus is strongly solvent dependent (see Table 16, *(63)—(65)*).

The ^{31}P chemical shift of *(61)* is indifferent to even drastic changes in solvent properties. For example, the strongly acidic alcohol, hexafluoroisopropanol does not influence the ^{31}P chemical shift of *(61)* appreciably.



(62) (63) (64) (65)

Table 16. The solvent dependence of the ^{31}P-NMR-spectrum [50] of some phosphorane derivatives (see [51a to 51h] in particular).

Compound	δ ^{31}P [a] in anhydrous solvents $CDCl_3$	DMF [b]	$(CF_3)_2CHOH$	$CDCl_3$ + $(CF_3)_2CHOH$ 2:1	1:1	δ ^{31}P in $CDCl_3$ + 1 mole equivalent water after $\frac{1}{2}$ h	after 24 h
(61)	+42.4 [c]	+41.2	+44.1 [d]	+42.3	+42.4	+42.0 [c]	+42.0
(62)	+49.7 [e]	+48.9	+48.3 [d]	+49.4	+49.6	+49.9 [e]	+49.8
(63)	+10.9	—	−96.8 [d, f]	+ 9.5	+ 9.0	−41.8 [g]	—
(64)	+44.7	—	—	—	—	—	—
(65)	+ 1.5	—	−85.3 [d, h]	−28.7	−53.4	−39.6 [d, g]	—

[*] *Note added in proof:* The variable temperature ^{1}H-NMR of *(61)* was accomplished in the range from ambient temperature to -155 °C in a 3:1 mixture of SO_2 and CF_2Cl_2 ("Freon 12") solvent system. In solution at ambient temperature the three methine protons give rise to one signal, an apparent doublet due to H—P coupling in the group H—C—O—P. The six methylene protons give rise to the usual signals associated with cyclohexane axial and equatorial hydrogens. Broadening of the signals occurs at $\sim -80°$ and coalescence occurs at $-120°$ (T_c).

This is consistent with a rapid positional exchange in *(61)* which is inhibited only at a relatively low temperature.

Ease of hydrolysis is a positive criterion for the tendency to undergo ring opening. Data in Table 16 evidence the stability of *(61)* towards water, excluding any measurable concentration of ring cleavage products.

It seems reasonable to counter the argument presented and conclude that the polycyclic oxyphosphorane derivatives *(59)—(69)* rearrange by rapid, *regular* processes with

relatively low energy barriers. For *ring strain reasons*, *e.g.* the fact that 6-membered rings prefer diequatorial sites, producing higher energy states if an apical-equatorial or diapical geometry is forced upon them (BPR requirement), the *BPR process can be ruled out*. In particular, in the case of *(61)* the observed rearrangement processes are unequivocally regular and can only proceed *via* TR or multiple TR pathways.

7. Analogous Rearrangement Processes of Compounds with Central Atoms Other than Phosphorus

Positional exchange processes in pentacoordinate molecules are not confined to phosphorus compounds as has been demonstrated earlier by the arsenic compounds *(51)—(55)*. Analogous rearrangements have been discussed for silicon[52] and sulfur compounds[53]. Pentacoordinate transition metal compounds such as $Fe(CO)_5$[54], $CF_3Co(CO)_3PF_3$[55], $CoH(PR_3)_4$[56], $IrH(CO)_2(PPh_3)_2$[57], $IrH(CO)_2(AsPh_3)_2$[57], $IrH(CO)_2(AsPh_3)_2$[57], and $IrH(CO)_2[P(p\text{-}F\text{—}C_6H_4)_3]_2$[57] undergo positional exchange.

Further, regular and irregular rearrangement processes are known for monocentric molecules for coordination numbers other than $n=5$. In fact, they exist for $n=3,\ldots,12$[58,59]. Hexacoordinate compounds such as $H_2Fe(PR_3)_4$[5c,56c,60] and $H_2Fe[C_6H_5P(OC_2H_5)_2]_4$[5c,60] as well as the metallocenes[61] deserve particular mention.

Mechanistic interpretation of all these rearrangements is best served by partitioning the pertinent symmetric permutation groups S_n into classes of conjugate elements, which correspond to the partitioning of the number n, and to further classify these on the basis of conjugation with regard to the skeletal symmetry[67] represented by G (see Section 3.2). This avoids the problem of overlooking relevant potential mechanisms.

In hexacoordinate molecules with O_h skeletal symmetry rearrangement by the "twist mechanism", a (3+3) TR mechanism, seems to be quite plausible. This was proposed long ago[62a] and a considerable amount of evidence has been published concerning it[62b]; however, it must be assumed that the 120° barriers are considerably higher in energy than the 60° barriers of comparable (2+3)-TR processes. These (3+3) and (2+3) mechanisms are related in the same manner as the conformational interconversion of ethane and the ethyl carbonium ion[63].

Metallocenes may be considered as hexacoordinate with respect to the orbital bond system[65]. We can also view them as decacoordinated if the C-atoms of the cyclopentadienyl systems are defined as the ligands. Analogously, the arene complexes such as dibenzene chromium[66] are hexacoordinate or dodecacoordinate respectively. In such compounds, the higher of the two coordination numbers determines the energy barriers for the process. Hence, the internal rotations of the metallocenes can be looked upon as (5+5)-TR processes and the analogous rearrangements of dibenzene metal complexes as (6+6)-TR mechanisms.

8. Conclusion

Discussions surrounding intramolecular rearrangement processes require a clear distinction between regular and irregular pathways, *i.e.* such processes which occur with preservation of ligands and coordination numbers and those proceeding with bond rupture and reformation *via* transition states or intermediates with varying coordination number. Regular processes require the presence of flexible mono or polycentric molecular skeletons. The systematic analysis of regular processes begins with the study of pertinent rigid skeletal models and their symmetries making use of the fact that skeletal flexibilities are representable by permutations which generally belong to subgroups of S_n. Skeletal equivalencies must also be treated. Direct products of these leads to the dynamic skeletal symmetry of a system. For the description of the "isolable" isomers (the classical species) of molecules with flexible skeletons one must employ the dynamic skeletal symmetry which permits differentiation between conformers as defined on the basis of rigid skeletal models. Conformers of a classical species are interconverted by skeletal flexibility operations, *i.e.* regular processes, whereas the classical species are interconverted only by irregular processes.

With this concept, one can recognize that rearrangements of molecules which proceed by deformations of bond angles at one center, such as the inversion of ammonia, the *syn-anti* isomerization of oximes, isomerizations of phosphoranes and the internal rotation of metallocenes, do not differ fundamentally from those conformational transformations in molecules with polycentric skeletons. This is true even though the latter rearrange by deformations of dihedral angles as illustrated in the rearrangements of ethane and cyclohexane derivatives and the pseudorotation of cyclopentane derivatives. Use of a collective term, interconversion of conformers, is suitable for all the above processes since it facilitates the uniform theoretical treatment they receive.

Formal mechanistic analysis of rearrangement processes among molecules whose skeletons carry n ligands can be achieved that are based upon the classes of conjugate elements of the symmetric group S_n by further subdividing these classes using the symmetries of the rigid skeletal models[67]. Physical constraints permit one to decide which of these classes and/or subclasses can correspond to regular processes as given by the skeletal flexibility and which of them can only represent irregular processes. A check against overlooking any possible mechanism is one distinct advantage provided by this systematic approach. Conclusions regarding the probability factor are made possible as well by considering the number of elements of a particular class of permutations.

Such an analysis of the conceivable reaction pathways for molecules with a pentacoordinate TBP skeleton indicates two types of regular processes are possible: (i) a purely vibrational process containing no relative internal rotation, and (ii) mechanisms which are primarily internal rotations, the simple and multiple TR processes.

Available experimental data suggest that the previously accepted thought that the BPR process, to the exclusion

of all alternatives (the TR mechanism was unknown until June 1970[4b]) is the best available mechanism for all pentatopal rearrangements is no longer tenable unless the definition of the BPR is altered to include the simple and multiple TR processes.

All of the pertinent data that can be interpreted by the BPR mechanism can also be interpreted by the equivalent TR process but the reverse is not true. There are observations whose interpretation by TR or multiple TR requires fewer additional hypotheses than required for explaining the same evidence on the basis of the BPR concept.

A decision of preference for one of a group of mechanistic alternatives not only requires information concerning energy barriers of the individual processes but also information about the probability factor. Our calculation data demonstrates that energy barriers for the BPR and TR processes are not sufficiently different to provide an unequivocal choice between the two. In some cases the BPR barrier seems favored (*e.g.* certain acyclic phosphoranes) while in other cases, the TR and multiple TR barriers are more attractive (*e.g.* some of the cyclic phosphoranes). TR processes are always favored statistically by at least a factor of 4 in single processes and by a factor of 4^n in a sequence of n single steps. Physically, this means that there is a narrow gap to pass at the barrier for BPR rearrangement while the TR mechanism offers a wide region to cross.

The present empirical data, in keeping with theoretical considerations, suggest that the regular rearrangements of cyclic pentacoordinate molecules proceed by the TR and/or multiple TR mechanism. Analogous acyclic systems can undergo rearrangements by either mechanism. In contrast to sequences of regular isomerizations containing exclusively BPR or single TR steps, reaction pathways employing multiple TR steps can, if necessary, bypass high energy TBP intermediates.

In this paper we have confined ourselves, for the most part, to a discussion of regular isomerizations of stable pentacoordinate phosphorane compounds. Regular and irregular rearrangements of phosphorane intermediates, essential for the understanding of the entire field of phosphorus chemistry, and, in particular, its biochemistry, will be discussed in a subsequent paper.

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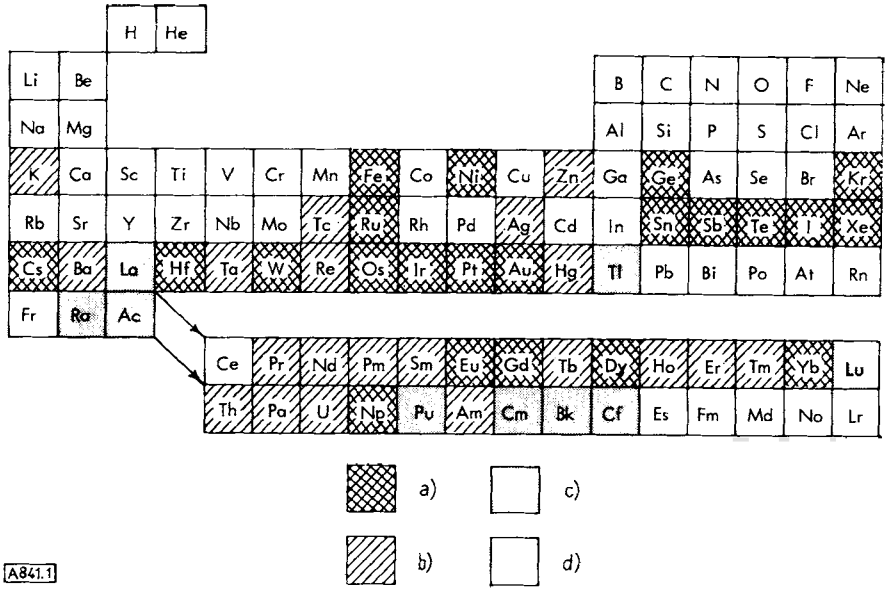
Applications of Mössbauer Spectroscopy to Problems in Solid-State Chemistry[**]

By Norman N. Greenwood[*]

The factors influencing the chemical isomer shift, quadrupole splitting and hyperfine magnetic interactions, are briefly summarized and applications to solid state systems reviewed. New results on the disordered rutile phases Fe_2MgF_6, $FeMg_2F_6$, *and* $FeCoNiF_6$, *and on the trirutile phase* $Li^+Fe^{2+}Fe^{3+}F_6$ *are presented to illustrate the power of the Mössbauer technique in probing details of oxidation states, site symmetries and magnetic ordering. An extensive study on the nonstoichiometric wüstite phase* $Fe_{1-x}O$ *is also reported and analyzed in terms of diffusion broadening at high temperatures and defect clustering in quenched samples; the production of essentially stoichiometric* FeO *by annealing is also discussed. Recent results on the application of large external magnetic fields to diamagnetic compounds of tin are reviewed and results of a Mössbauer investigation of lunar samples returned by the Apollo 11 and 12 missions are discussed.*

1. General

The Mössbauer effect is the recoilless emission and resonant reabsorption of γ-rays. Its importance lies in the production of extremely monochromatic radiation which can be used as a spectroscopic source of energy to probe details of chemical structure and bonding. The underlying theory has been outlined by *R. L. Mössbauer*[1a] in a previous article and has been extensively reviewed[1b]. The effect has so far been demonstrated in 72 isotopes of 42 different elements as indicated in Fig. 1. It can be seen that Mössbauer spectroscopy is potentially a widely applicable technique particularly among the heavier elements.



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The precise energy of the resonant transition is influenced by three hyperfine interactions which form the basis of its use in solid-state chemistry. The first of these interactions gives rise to a *chemical isomer shift*, δ, and originates in the varying coulombic interaction between the positive nucleus of an atom and its electronic environment. The chemical isomer shift is directly proportional both to the change in nuclear radius on excitation, $\delta R/R$, and to the change in s electron density at the nucleus on going from the source to the absorber. Its magnitude is determined by the following factors:

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2. Shielding effects of p, d, and f electrons on the s-electron density at the nucleus
3. Covalency effects in modifying s, p, and d electron population and distribution, including
   (a) σ withdrawal of electrons by electronegative groups
   (b) deshielding due to d_π back bonding

Some examples of the dependence of chemical isomer shift on oxidation state are given in Fig. 2 which plots observed ranges of δ for four typical Mössbauer isotopes ^{57}Fe, ^{127}I, ^{129}Xe, and ^{237}Np. This shift finds many applications in solid-state chemistry as a rapid, non-destructive probe of oxidation state in minerals and nonstoichiometric compounds. For example the Mössbauer systematics of a variety of metal sulfides of known structure enabled the oxidation state of iron and tin in several sulfide minerals to be unambiguously determined. It was found[2], *e.g.*, that

chalcopyrite is $Cu^+Fe^{3+}S_2^{2-}$, not $Cu^{2+}Fe^{2+}S_2^{2-}$;
cubanite is $Cu^+(Fe^{2+}Fe^{3+})S_3^{2-}$, not $Cu^{2+}Fe_2^{2+}S_3^{2-}$;
stannite is $Cu_2^+Fe^{2+}Sn^{4+}S_4^{2-}$, not $Cu^+Cu^{2+}Fe^{3+}Sn^{2+}S_4^{2-}$
etc.

$(SO_4^{2-})_3$. Variations in the conditions of preparation lead to some replacement of titanium by iron, the actual composition being $Fe_{1+x}Ti_{1-x}(SO_4)_3$; the Mössbauer spectra in such cases showed that the detailed formulation of the stoichiometry was $(Fe^{2+}_{1-x-y}Fe^{3+}_{x+y})$ $(Fe^{3+}_xTi^{3+}_yTi^{4+}_{1-x-y})$ $(SO_4^{2-})_3$ and an analysis of peak areas gave a measure of the relative concentrations of Fe^{2+} and Fe^{3+}

Another area in which Mössbauer spectroscopy has proved particularly useful is in determining oxidation states after nuclear reactions. Thus[4] irradiation of $MgSnO_3$ with thermal neutrons produces appreciable amounts of Sn^{II} which can subsequently be removed by oxidative annealing in air. There is now an increasing amount of work being published on the use of Mössbauer spectroscopy for the study of radiation damage in solids and for the investigation of radioactive decay after-effects on the submicrosecond time scale[5].

The second hyperfine interaction from which information can be obtained is the quadrupole splitting, Δ. Any nuclear state with a spin quantum number $I > \frac{1}{2}$ has a quadrupole moment Q, which can interact with an electric field gradient,

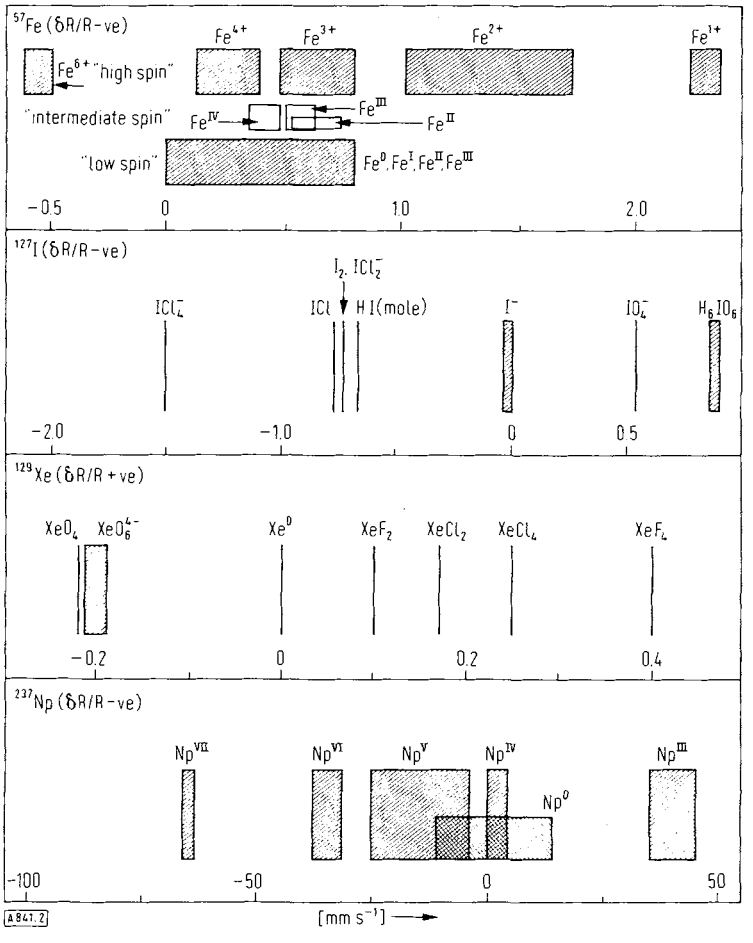


Fig. 2. Range of chemical isomer shift for ^{57}Fe, ^{127}I, ^{129}Xe, and ^{237}Np as a function of oxidation state and spin multiplicity.

Likewise the unusual blue color of the readily synthesized compound of ideal composition $FeTi(SO_4)_3$ was traced to the presence of both Fe^{2+} and Fe^{3+} in the compound which should be formulated[3] $(Fe^{2+}_{1-y}Fe^{3+}_y)$ $(Ti^{3+}_yTi^{4+}_{1-y})$

q, to lift the degeneracy of the state. In the simplest case of a transition between $|\pm\frac{3}{2}\rangle$ and $|\pm\frac{1}{2}\rangle$ in an axially symmetric electric field gradient the quadrupole splitting, Δ, is directly proportional to both Q and q. In general, it has been found

that Δ is an extremely powerful probe of local site symmetry and its magnitude has been found to depend on:

1. Electronic configuration of the atom, including
   (a) oxidation state
   (b) spin multiplicity
2. Site symmetry, including effect of
   (a) coordination number
   (b) *cis-trans* isomerism
   (c) ligand-field distortions *etc.*
3. Contributions from neighboring charges (atoms or ions)
   (a) asymmetric withdrawal of p and d electrons for bonding
   (b) polarizable atoms in covalent assemblies
   (c) lattice terms in ionic crystals

The third hyperfine interaction which influences the Mössbauer spectrum is the nuclear magnetic Zeeman splitting which arises when the nucleus is subject to an internal or an applied magnetic field. The extent of the energy separation depends both on the nuclear magnetic moments of the ground and excited states, and also on the magnitude of the magnetic field H. Thus in ^{57}Fe the $|\pm\frac{1}{2}\rangle$ ground state splits into two sublevels and the $|\pm\frac{3}{2}\rangle$ excited state splits into four sublevels; transitions between these are normally subject to the selection rules $\Delta m = 0, \pm 1$, so that six resonance lines will be seen. If an electric field gradient is also present then there is a perturbation which disturbs the even spacing of the lines and enables the mutual orientation of H and q to be determined.

2. Investigations on Metal Fluoride Systems

We have recently been using the above mentioned hyperfine interactions to study the details of structure and bonding in several fluoride phases having the rutile structure (Fig. 3). Thus, the Mössbauer spectra of FeF_2, Fe_2MgF_6, $FeMg_2F_6$, and $FeCoNiF_6$ all show a sharp quadrupole-split doublet with no indication of line broadening whatsoever[16]. This implies a statistical disordering of the various cations on the available cation sites. Further, as the cations have similar radii and identical charge, the positions of the six fluoride ions surrounding each metal remain unaltered; as the influence of this distorted octahedron on the high-spin Fe^{2+} d^6 configuration is the principal source of the electric field gradient in these compounds, the constancy of Δ and the sharpness of the lines can be understood. Below the Néel temperature these four compounds become antiferromagnetic and the spectra (Fig. 4) are characterized by a six-line pattern with two weak additional lines due to the usually forbidden transitions $|+\frac{3}{2}\rangle \rightarrow |-\frac{1}{2}\rangle$ and $|-\frac{3}{2}\rangle \rightarrow |+\frac{1}{2}\rangle$ which become allowed when magnetic and quadrupole interactions are mixed.

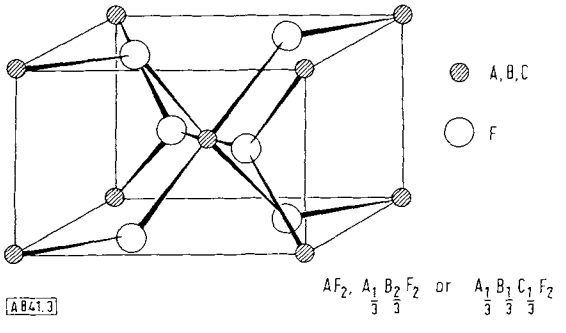


Fig. 3. The rutile structure of FeF_2 and several disordered ternary and quaternary fluoride phases such as Fe_2MgF_6, $FeMg_2F_6$, and $FeCoNiF_6$.

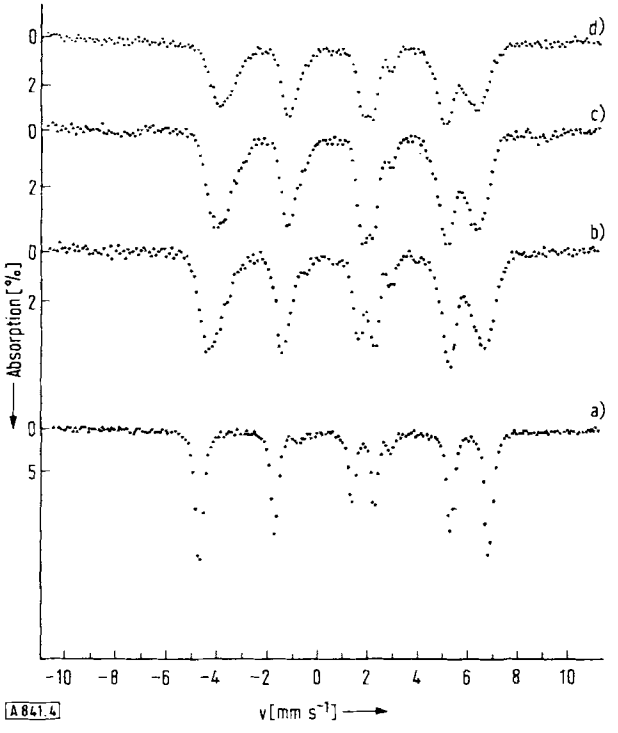


Fig. 4. Mössbauer spectra of a) FeF_2, b) Fe_2MgF_6, c) $FeMg_2F_6$, and d) $FeCoNiF_6$ at 4.2 K.

Another feature of these spectra is the appreciable broadening of the outer lines as compared with the spectrum of FeF_2 itself; this arises from a range of hyperfine magnetic fields which in turn reflects the range of (magnetic) local environments. The results indicate how fine a probe the technique is of local environment in the presence of statistical disorder.

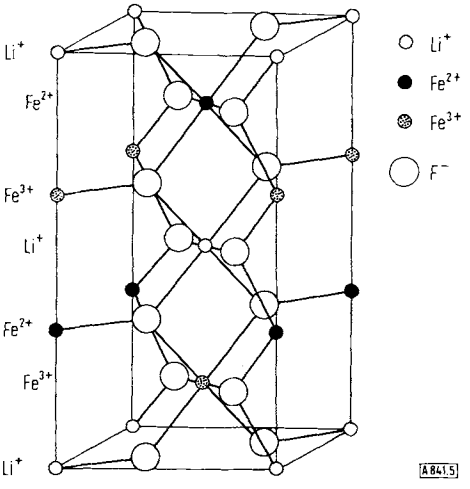


Fig. 5. The trirutile structure of $LiFe_2F_6$.

A particularly interesting compound of a related type is $LiFe_2F_6$. X-ray powder data had shown that the compound has the trirutile structure (Fig. 5) but was unable to distinguish between Fe^{2+} and Fe^{3+} and so left unanswered the question as to whether these ions were statistically disordered between the layers of lithium ions, or indeed whether the ions had a separate existence rather than being subject to rapid electron hopping or interchange. The Mössbauer technique is ideally suited to answer these questions and has yielded the following results[6, 7]:

(a) Fe^{2+} and Fe^{3+} give separate resonances at all temperatures up to the decomposition point of the compound (≈ 1000 K) indicating that there is no rapid electron hopping between the two species within the lifetime of the ^{57}Fe excited state (97 ns)

(b) The magnetic spectra below the Néel temperature of 102 K show two separate, sharp, magnetic hyperfine spectra arising from Fe^{2+} and Fe^{3+}, respectively. The sharpness of the lines implies that both the geometric and magnetic environments of each Fe^{2+} and Fe^{3+} ion are identical so that there is an ordering of all three cations Li^+, Fe^{2+}, and Fe^{3+} into every third layer respectively, as shown in Fig. 5.

(c) The Fe^{2+} and Fe^{3+} magnetic moments are aligned ferrimagnetically within each trirutile layer and the net moments are then aligned antiferromagnetically between successive layers.

3. Investigations of Metal Oxide Systems

If we now turn from fluoride systems to oxide systems we find that a vast range of problems has been studied by Mössbauer spectroscopy. Much of this has already been extensively reviewed[1, 5] and the resulting systematics have proved of considerable diagnostic value. The main observations are as follows:

(a) The chemical isomer shift of high-spin Fe^{3+} is substantially smaller than for high-spin Fe^{2+} by ≈ 0.8 mm s^{-1};

(b) The chemical isomer shift for iron in tetrahedral environments is somewhat smaller than for octahedral coordination; hence δ (tetrahedral Fe^{3+}) $< \delta$ (octahedral Fe^{3+}) $< \delta$ (tetrahedral Fe^{2+}) $< \delta$ (octahedral Fe^{2+});

(c) The quadrupole splitting, Δ, for both Fe^{3+} and Fe^{2+} in sites of accurately cubic symmetry is zero;

(d) For non-cubic sites $\Delta(Fe^{3+}) < \Delta(Fe^{2+})$;

(e) The magnetic hyperfine field $H(Fe^{3+}) > H(Fe^{2+})$.

Application of these generalizations has proved particularly valuable in studying the oxidation states, site occupancy, and degree of inversion of spinel phases[8]. Some of the results are summarized in Tables 1 and 2.

Table 1. Mössbauer spectra of ferrous spinels [*].

Spinel type	Site occupied	Example	Spectrum	Remarks
normal 2,3	A	$Fe^{2+}[Cr_2^{3+}]O_4$	single line $\Delta = 0.0$, $\delta = 0.83$	tetrahedral site has cubic symmetry; phase becomes tetragonal below 135 K ($\Delta \neq 0$) and ferrimagnetic below 69 K.
normal 4,2	B	$Ge^{4+}[Fe_2^{2+}]O_4$	two lines $\Delta = 2.80$, $\delta = 1.12$	large e.f.g. (q) from trigonal distortion on d^6; phase becomes antiferromagnetic below 11 K.
partly inverse 2,3	A and B	$Fe_x^{2+}\,Ga_x^{3+}[Fe_x^{2+}\,Ga_{2-x}^{3+}]O_4$	two pairs of lines $\Delta_A = 1.2$, $\delta_A = 0.83$ $\Delta_B = 2.9$, $\delta = 0.9$	non-cubic A site due to charge variations on B site; trigonal distortion at B site. Note A site has the smaller Δ and lower δ.

[*] δ in mm s^{-1} relative to iron foil; Δ in mm s^{-1}; H in kG.

Table 2. Mössbauer spectra of ferric spinels [*].

Spinel type	Site occupied	Example	Spectrum	Remarks
disordered 2,3	A	$Fe^{3+}[Ni^{2+}Al^{3+}]O_4$	two lines $\Delta = 0.53$, $\delta = 0.18$	cation disorder on B sites removes cubic symmetry of A sites
normal 2,3	B	$Zn^{2+}[Fe_2^{3+}]O_4$	two lines $\Delta = 0.36$, $\delta = 0.37$	e.f.g. (q) from trigonally distorted B site acting on spherical d^5
inverse 2,3	A and B	$Fe^{3+}[Cu^{2+}Fe^{3+}]O_4$ (tetragonal)	two superimp. six-line spectra A: $\delta = 0.33$, $H = 478$ $\varepsilon = 0.00$ B: $\delta = 0.50$, $H = 514$ $\varepsilon = 0.14$	only B site shows quadrupole effect ($\varepsilon = 0$ for A site may depend on alignment of e.f.g. (q) and H); A site has the smaller H and lower δ

[*] δ in mm s^{-1} relative to iron foil; Δ in mm s^{-1}; H in kG.

In favorable cases Mössbauer spectroscopy can be used to study not only the details of the static structure of a solid-state system but can also be used to investigate lattice dynamics, diffusion and reaction rates. Before con-

sidering specific examples it is necessary to realize that, depending on the timescale of the motions, vibration, diffusion, and jumping affect the Mössbauer resonance in different ways[9].

If the nucleus of interest is undergoing harmonic vibration about a fixed site at a frequency which is high compared with the inverse excited-state lifetime then this simply produces a reduction in intensity of the resonance without any line broadening, the decrease in the recoilless fraction f being given by the Debye-Waller formula

$$f = e^{-4\pi^2 x^2/\lambda^2}$$

where x^2 is the mean square amplitude of oscillation in the direction of observation of the γ-ray and λ is the wavelength of the γ-photon. This means that values of x of the order of 10 pm are conveniently measurable with Mössbauer isotopes having excited-state lifetimes similar to those of ^{57}Fe or ^{119}Sn.

A second limiting case arises if the nucleus of interest is undergoing continuous diffusion or Brownian motion. This leads to a broadening of the Mössbauer line with no reduction in overall recoilless fraction and no change in the basic Lorentzian line shape. This energy broadening, $\Delta\Gamma$, expressed as an increase in the linewidth at half height, is given by

$$\Delta\Gamma = 2\hbar\left(\frac{2\pi}{\lambda}\right)^2 D$$

where D is the self-diffusion coefficient. Values of D of the order of 10^{-15} m^2 s^{-1} give broadenings of the order of the natural linewidth for ^{57}Fe or ^{119}Sn resonances.

The third limiting case concerns jump diffusion. If the resonant nuclei jump instantaneously between fixed sites in such a way as to produce a random phase shift in the γ-ray wave train at each jump, then, as in the preceding case, the line is broadened without reduction in the recoilless fraction and without loss of the Lorentzian line shape; under these conditions the broadening is given by

$$\Delta\Gamma = 2\hbar/\tau_0 = 12\hbar D/l^2$$

where τ_0 is the mean resting time between jumps, D is the self diffusion coefficient and l^2 the mean square jump distance. Values of τ_0 equal to 280 ns and 53 ns give broadenings equal to the natural linewidth for ^{57}Fe and ^{119}Sn respectively.

An example of this last mechanism is afforded by the wüstite phase $Fe_{1-x}O$ at high temperatures and we have recently been studying this in some detail[7]. The work required the construction of a Mössbauer sample holder which could be held at various temperatures up to 1300 K under controlled partial pressures of oxygen down to 10^{-16} N m^{-2} whilst still being transparent to the 14.4 keV γ-rays[10]. Typical spectra are shown in Fig. 6 for various temperatures and compositions. The first spectrum which refers to a sample at the iron-rich phase boundary at 1168 K shows a resonance which can be resolved into two components: a narrow line, due to metallic iron above its

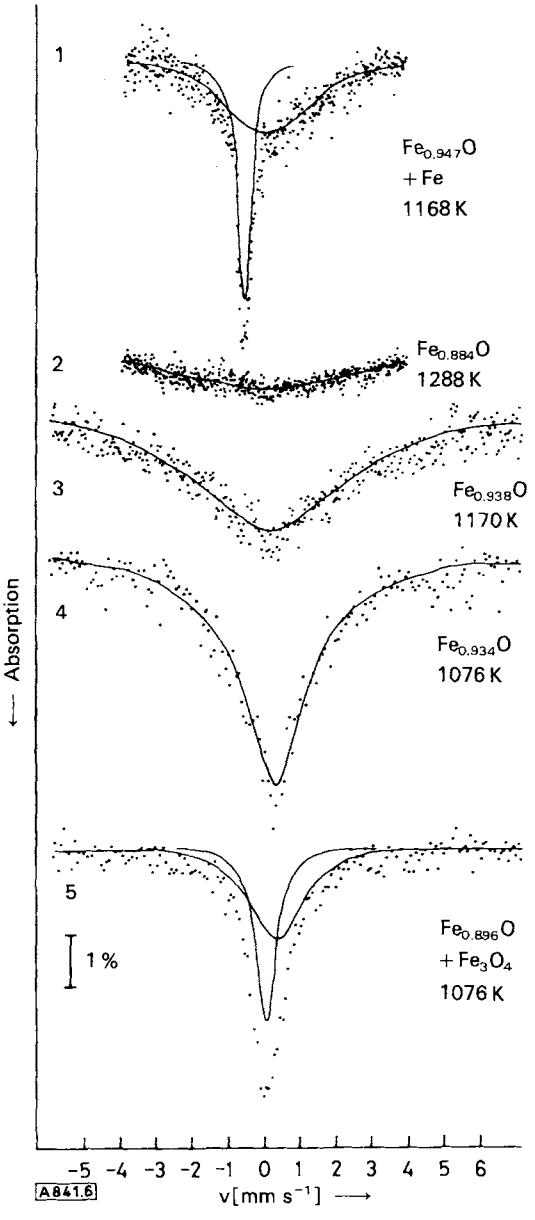


Fig. 6. Diffusion-broadened Mössbauer spectra of $Fe_{1-x}O$ under equilibrium conditions. At the phase boundaries sharp peaks due to Fe (sample 1) and Fe_3O_4 (sample 5) are also present.

Curie temperature, and a broad resonance due to the oxide phase. Spectrum 2 illustrates a typical resonance obtained from $Fe_{0.884}O$ at an even higher temperature 1288 K; the single resonance is now nearly 25-times the natural linewidth as a result of diffusion broadening. Spectra 3 and 4 illustrate the effect of temperature on samples of composition $Fe_{0.938}O$ and $Fe_{0.934}O$; the drop in temperature from 1170 K to 1076 K decreases the resonance linewidth by a factor of more than two. Finally, at the oxygen rich end of the wüstite phase field, spectrum 5 illustrates the resonance at 1076 K comprising a fairly narrow line due to Fe_3O_4 above its Néel temperature and a broadened resonance from $Fe_{0.896}O$. Several important results emerge from this study of $Fe_{1-x}O$. Firstly, the absolute values of the diffusion coefficients, when calculated from the theory of *Singwi* and *Sjölander*[11] were in excellent agreement with those reported from a previous study using the radioactive tracer technique[12]. The work therefore establishes the Möss-

bauer method as a valuable technique for studying diffusion in polycrystalline oxide samples at temperatures several hundred degrees below the melting point; previously the method had only been applied to diffusion in metals near the melting point. The technique is particularly valuable because it is independent of bulk transport, and because it is independent of other phases present as well as being independent of cracks or grain boundaries. Further, as the effect does not vary with time the sample can be fully equilibrated at the required temperature and pressure before measurements are begun.

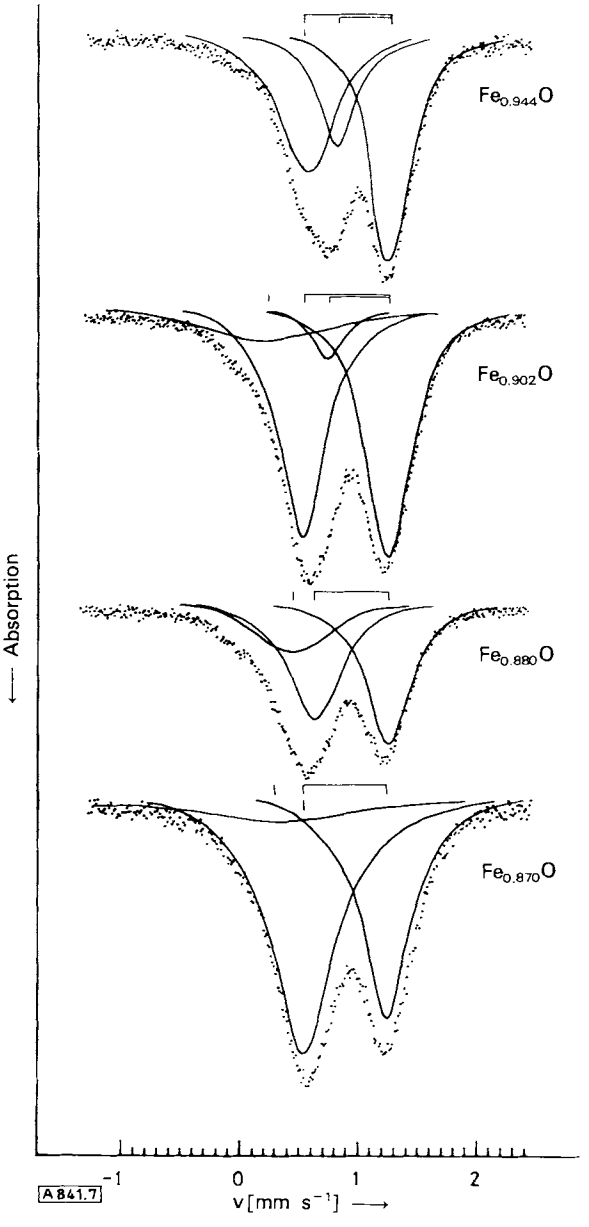


Fig. 7. Typical room-temperature Mössbauer spectra of quenched samples of $Fe_{1-x}O$ and proposed analysis in terms of two Fe^{2+} doublets and a broad Fe^{3+} resonance.

A second important result of the study was that at 1075 K the line broadening, and hence the diffusion coefficient were independent of composition (defect concentration). This implies an association of vacant cation sites and Fe^{3+} ions and has led to a detailed structure of the defect cluster in $Fe_{1-x}O$ at high temperatures[10]. At temperatures above 1100 K the line broadening becomes increasingly dependent on phase composition, implying a partial dissociation of the defect clusters.

When samples of $Fe_{1-x}O$ which have been equilibrated at high temperature are quenched very rapidly to room temperature the single broadened line splits into a partially resolved envelope of several overlapping resonances. Typical examples are shown in Fig. 7 for a variety of compositions. By studying the variation of line shape and intensity as a function of composition, and by doing a full statistical analysis of all possible model component spectra it was shown that the spectra were best considered as a pair of overlapping doublets from Fe^{2+} and a broader unresolved resonance from Fe^{3+}. There was no evidence for averaging of parameters by electron exchange between Fe^{2+} and Fe^{3+} and it is also significant that there was not a *range* of quadrupole splittings for Fe^{2+} at each composition but only two. The most obvious interpretation of these results is again in terms of defect clusters; it is then possible to assign the Fe^{2+} spectra respectively to Fe^{2+} adjacent to a defect cluster and Fe^{2+} further removed from the cluster, whilst the Fe^{3+} envelope embraces both tetrahedral and octahedral sites. This model not only gives the best statistical fit to the data but also gives concentrations of Fe^{2+} and Fe^{3+} which parallel the known composition over the whole range of samples from $Fe_{0.88}O$ to $Fe_{0.94}O$.

A further novel effect was also investigated during this study on quenched $Fe_{1-x}O$. When samples of the type discussed in the preceding paragraph are annealed for a few minutes at temperatures in the region of 500 K (or at temperatures above or below this) the broad quadrupole split Mössbauer spectra shown in Fig. 7 undergo a dramatic change—the linewidth progressively narrows to give a single sharp resonance approaching natural linewidth in the region expected for Fe^{2+} in a purely cubic environment. At the same time weaker components corresponding to the spectrum of Fe_3O_4 begin to appear (see Fig. 8)[10]. The position of the new narrow resonance is independent of

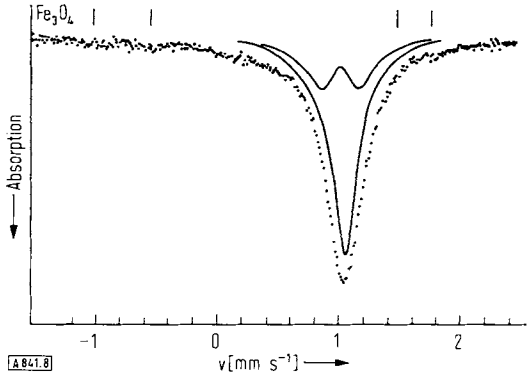


Fig. 8. Spectra of partly annealed (20 min at 300 °C) $Fe_{0.944}O$ showing the single sharp resonance of essentially stoichiometric FeO and the incipient emergence of the four inner peaks of Fe_3O_4 formed during disproportionation.

the original composition of the quenched wüstite phase but the relative intensities of this line and the Fe_3O_4 lines depend directly on the composition. This, in conjunction

with the implied precise cubic symmetry of the main Fe^{2+} site strongly implies disproportionation of the wüstite phase into essentially stoichiometric FeO and Fe_3O_4; this conclusion is confirmed by the measurement of the lattice constant a_0 of the new phase which corresponds precisely with the extrapolated value expected for a composition $Fe_{1-x}O$ in which $x = 0.00 \pm 0.01$. Thus

$$Fe_{1-x}O = (1 - 4x)\,Fe_{1.00}O + x\,Fe_3O_4$$

This is striking independent evidence for the formation of essentially stoichiometric FeO by a disproportionative mechanism as first proposed by *Hoffmann*[13]. Further evidence consistent with this view was obtained from the well resolved hyperfine field of Fe^{2+} in cubic environment below the Néel temperature. It is clear that this detailed study of quenched and annealed samples of FeO, as well as the equilibrium study of the wüstite phase field at high temperatures has added greatly to our understanding of this classic nonstoichiometric oxide.

4. Application of a Strong External Magnetic Field on Diamagnetic Tin Compounds

Another aspect of our recent work is the measurement and interpretation of ^{119}Sn Mössbauer spectra in the presence of applied superconducting magnetic fields at 4.2 K. Such work gives information about the sign of the quadrupole interaction and hence helps in the elucidation of the origin of this interaction in tin compounds. The problem is more complex than that of magnetic and quadrupole interactions in ^{57}Fe because the excited state of ^{119}Sn has a smaller quadrupole moment than that of ^{57}Fe whereas the nuclear magnetic moments of both the ground and excited state of ^{119}Sn are appreciably larger than those for ^{57}Fe. The data are in Table 3. One consequence of this, coupled with the rather large natural linewidth of the ^{119}Sn resonance,

Table 3. Nuclear quadrupole and magnetic moments [*] for the ground state and first excited state of ^{57}Fe and ^{119}Sn.

Nucleus	Q_g (barn)	Q_e (barn)	μ_g (μ_N)	μ_e (μ_N)
^{57}Fe	0	+0.33	+0.09024	−0.1547
^{119}Sn	0	−0.07	−1.046	+0.70

[*] 1 barn = 10^{-28} m^2
1 nuclear magneton = 5.050×10^{-27} A m^2

is that only limiting cases in which Δ is either zero or very large can be readily interpreted by simple perturbation theory. These two limiting cases are illustrated in Figs. 9 and 10 which show that when $\Delta \simeq 0$ mm s^{-1} as in SnO_2 an applied magnetic field gives rise to an unresolved doublet of triplets whereas when $\Delta = 4.2$ mm s^{-1} (as in Me_2SnMoO_4) the spectrum comprises a high field doublet and a lowfield quartet[14]. For intermediate cases (*e.g.* Me_2SnCl_2 for which $\Delta = 3.4$ mm s^{-1}) the pattern is more complex and the applied field cannot be treated as a simple perturbation of the quadrupole interactions. In such cases the total hyperfine interaction Hamiltonian must be in-

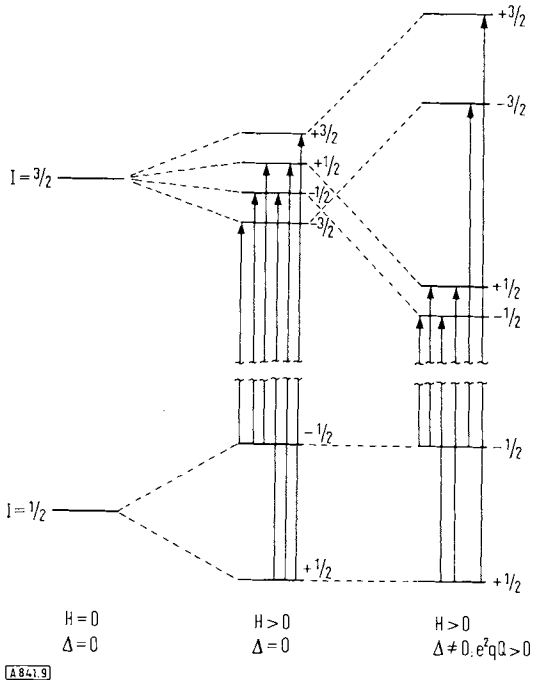


Fig. 9. Energy levels for the ^{119}Sn nucleus in the presence of magnetic and combined magnetic and quadrupolar interactions.

corporated into the treatment. Without this the experimental results are unintelligible, particularly for moderately small quadrupole splittings and applied magnetic fields. As an aid to the visual interpretation of such spectra *T. C. Gibb* in our Laboratories has computed an atlas of theoretical spectra to be expected for powdered samples in magnetic fields applied either perpendicular or parallel to the γ-ray direction and for a wide range of quadrupole

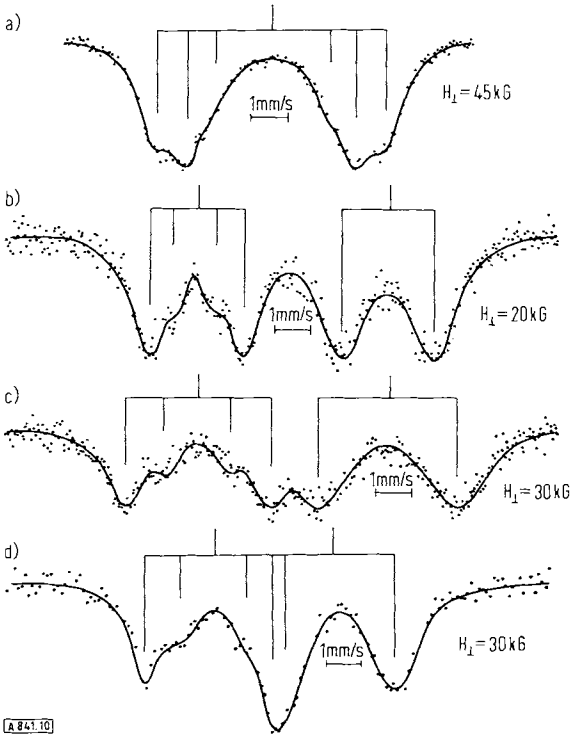


Fig. 10. Mössbauer spectra of tin compounds in the presence of an external magnetic field perpendicular to the direction of observation of the γ-rays: (a) SnO_2, (b) and (c) Me_2SnMoO_4, (d) Me_2SnCl_2.

splittings[15]. Typical spectra are shown in Figs 11 and 12. The results are particularly valuable in helping to design experiments since they indicate the optimum value of the magnetic field for a particular compound and also indicate the optimum setting for the velocity scan of the spectrometer. They also permit immediate visual determination of the sign of the electric quadrupole interaction e^2qQ and hence the sign and probable origin of the electric field gradient q. In this way we have shown[16] that e^2qQ is positive for the tin(II) compounds SnO, SnS, SnF_2, SnC_2O_4 and $Sn_3(PO_4)_2$ despite some contradictory claims in the literature; this demonstrates the dominating influence of the p_z character of the lone-pair electrons in these compounds. Likewise the *trans*-octahedral complex Me_2SnF_2 has positive e^2qQ whereas the trigonal pyramidal Me_3SnNCS and Me_3SnOH have negative e^2qQ because, in each case, of the dominating effect of the electrons in the Sn—C bonds when compared with the lower electron density near the tin atom in the bonds to electron-withdrawing groups such as F and OH[17]. Results on numerous other tin(IV) compounds in an applied magnetic field are consistent with these conclusions[17]

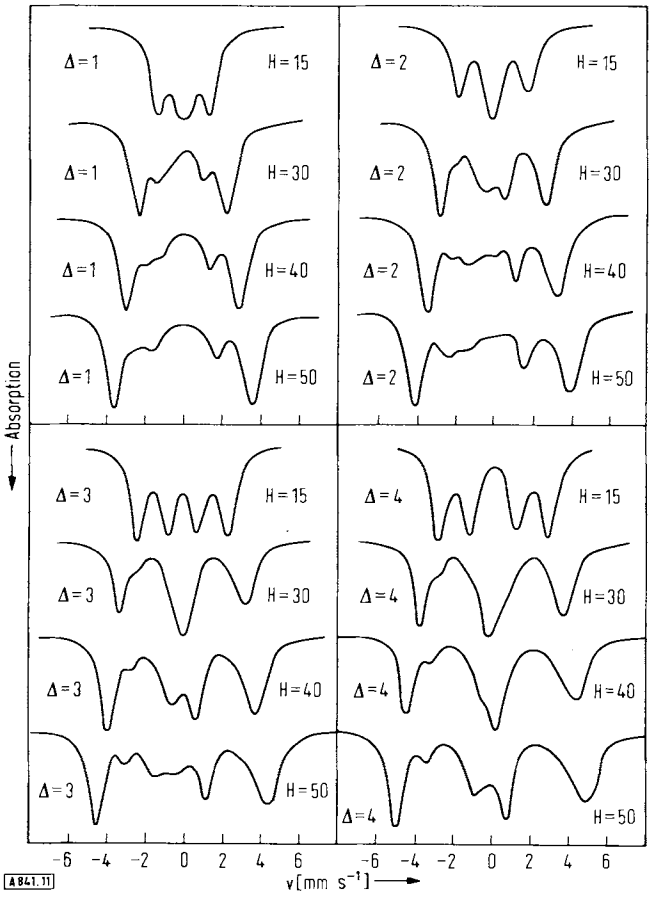


Fig. 11. Calculated spectra for ^{119}Sn with varying values of the quadrupole splitting Δ mm s^{-1} and magnetic field H (kG). In all cases H is parallel to the direction of observation, e^2qQ is positive, the asymmetry parameter $\eta = 0$, and the resonance linewidth has been taken to be 0.8 mm s^{-1}.

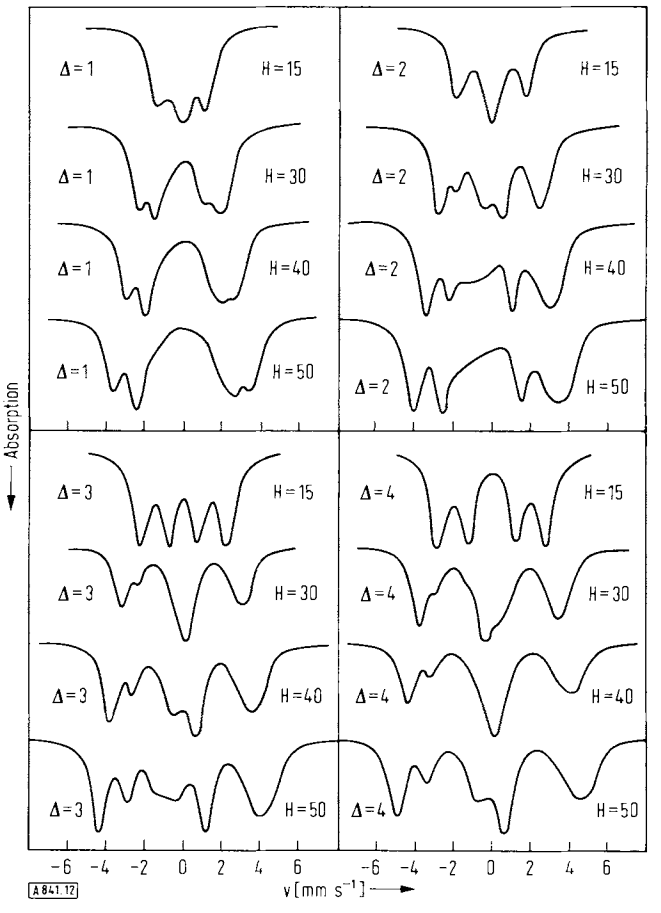


Fig. 12. Calculated spectra as for Fig. 11 but with H perpendicular to the direction of observation.

5. Investigations on Lunar Samples

In the last part of this article some recent work we have been doing on the application of Mössbauer spectroscopy to the analysis of the Lunar Samples returned by Apollo 11 and 12 last year will be outlined. Preliminary analysis[18] showed that the only Mössbauer isotope present in sufficient concentration in samples of the lunar regolith was ^{57}Fe. A typical spectrum of unseparated fines is reproduced

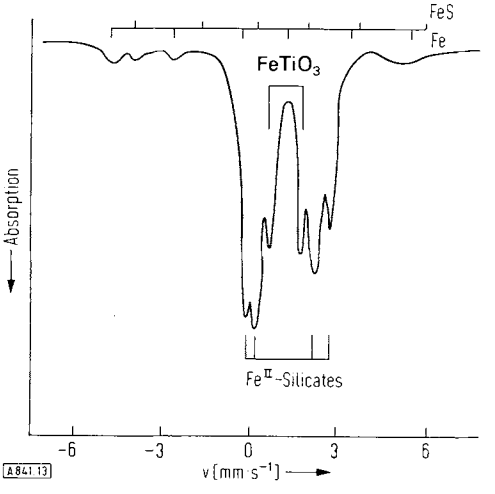


Fig. 13. Room-temperature Mössbauer spectrum of lunar microbreccia from the Apollo 11 mission.

in Fig. 13; it shows the presence of traces of metallic iron and troilite, and larger concentrations of ilmenite and Fe^{II} silicate phases, but there is no evidence for Fe^{III} or any other oxidation state of iron. More detailed work at various temperatures and under higher resolution led to the results in Table 4[19].

Table 4. Mössbauer data [*] and assignments for lunar fines (10084—13).

Chemical isomer shift (mm s^{-1}) [*]		Quadrupole splitting (mm s^{-1})		Assignment	% of resonance by area at
290 K	80 K	290 K	80 K		80 K
1.1	1.19	0.7	1.1	ilmenite (A)	20
1.2	1.21	2.0	2.1	glasses and site M 2 of clinopyroxenes (B)	75
1.2	1.31	2.5	2.9	olivines and site M 1 of clinopyroxenes (C)	
	0.0	($H = 330$ kG)		Fe (metal)	4
	0.9			FeS (troilite)	≤1

[*] With respect to metallic iron at 290 K as zero.

Phases definitely identified include native iron, troilite (stoichiometric FeS), ilmenite ($FeTiO_3$), clinopyroxenes [$Ca(Mg,Fe)Si_2O_6$], olivines [$(Mg,Fe)_2SiO_4$], and high spin Fe^{2+} in glassy silica phases. The data illustrate again the great range of information which can be obtained rapidly and nondestructively from small samples of unknown constitution. The results have been confirmed by other groups of workers[20], and have proved particularly valuable in helping to elucidate the complex magnetic properties of lunar minerals[21]. In addition a careful determination of the Néel temperature of lunar ilmenite showed it to be 57 ± 2 K in agreement with the known value for stoichiometric terrestrial ilmenite $FeTiO_3$[20].

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Synthesis of Octakis(trifluorophosphane)-diiridium[1]

By *Thomas Kruck, Gerd Sylvester,* and *Inge-Petra Kunau*[*]

Mononuclear metal(0)-trifluorophosphane complexes $M(PF_3)_n$ of chromium, iron, nickel, and all their homologs have been synthesized in recent years[2]. Meanwhile only two homogeneous dinuclear complexes $[M(PF_3)_n]_2$ (M=Re: $n=5$; M=Rh: $n=4$) containing a direct metal-metal bond have been isolated for transition metals of odd atomic number[3,4], in sharp contrast to the situation in the chemistry of metal carbonyls. The reason for this behavior in the case of the cobalt group may be seen in the ease of formation of the highly stable hydrides $HM(PF_3)_4$ (M = Co, Rh, Ir); they are even formed under the conditions of reductive trifluorophosphanation of metal salts in the presence of slight traces of hydrogen-containing substances.

We have now succeeded in preparing and characterizing the first diamagnetic and thus dinuclear trifluorophosphane complex of iridium(0) by elimination of hydrogen from tetrakis(trifluorophosphane)iridium hydride *(2)*: Octakis-(trifluorophosphane)diiridium *(1)*, whose existence can be predicted by the noble gas rule, is formed in about 20% yield according to equation (1) on UV-irradiation of an ethereal solution of *(2)* for 17 hours.

$$\underset{(2)}{2\,HIr(PF_3)_4} \xrightarrow{\text{UV light}} \underset{(1)}{(PF_3)_4Ir{-}Ir(PF_3)_4} + H_2 \qquad (1)$$

The bright yellow crystals left on removal of the solvent melt at 105 °C and sublime at 20 °C/10^{-3} torr. They dissolve in all the common organic solvents and are stable for some time in air. IR spectroscopy showed that the prolonged action of even the slightest trace of moisture eventually leads to formation of the hydride *(2)*. The vapor-phase IR spectrum of *(1)* shows two sharp bands at 939 (w) and 900 (m) cm^{-1} which lie in the characteristic P—F stretching frequency range. As expected they are shifted to shorter wavelengths compared with *(2)*.

The ^{19}F-NMR spectrum (KIS-2, 84.7 MHz, dissolved in ether at 25 °C) shows only a doublet at $\delta = 5.85$ ppm (Cl_3CF as external standard); nor do any further signals appear at higher amplification, thus ruling out the presence of a PF_2 bridge such as is formed in the corresponding photolysis of $HCo(PF_3)_4$ to $(PF_3)_3Co(PF_2)(H)Co(PF_3)_3$[5]. The coupling constant $^1J_{P-F}$ of 1238 Hz lies in the usual region for terminal PF_3 groups.

The mass spectrum (Atlas CH 4, 20 and 70 eV) affords conclusive proof of the presence of an Ir—Ir bond. The molecular weight is apparent from the molecular peak at $m/e = 1088$. Fragmentation is characterized by two reactions: 1) Successive loss of PF_3 groups and 2) rupture of the Ir—Ir bond followed by loss of PF_3 from the two halves of the molecule. The higher the energy, the greater the role played by the second fragmentation route.

In line with the simple IR spectrum and the magnetic equivalence of the fluorine atoms, the following structure is proposed for *(1)*: The molecule is made up of two trigonal bipyramids, each Ir atom occupying the central position of one pyramid and the axial position of the other. Magnetic equivalence of the F atoms in this case results from structural isomerization or virtual coupling. We regard as unlikely a structure in which the Ir atoms occupy the apices of two square pyramids and are linked together such that the planes of the PF_3 groups are parallel to each other.

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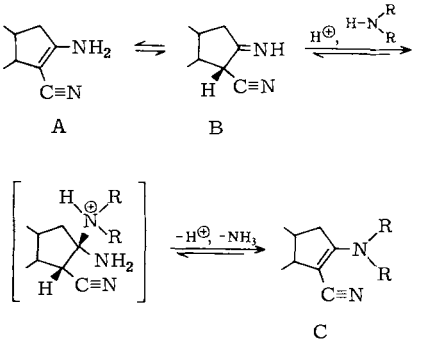
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Transamination of Cyano Enamines[**]

By *Reinhard Helmers*[*]

Thorpe-Ziegler cyclization of dinitriles affords cyclic cyano enamines A whose tautomers—the imino compounds B—are hardly detectable[1]. Interest in these compounds was hitherto limited mainly to their hydrolysis reactions. As a hetero ketone analog, compound B should undergo proton-catalyzed condensation with secondary amines to give the enamines C, like the corresponding ketones.

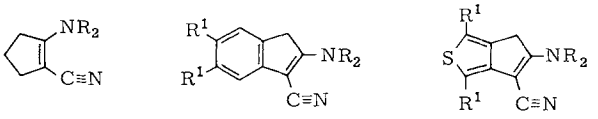


Only two instances of this exchange reaction have so far been recorded in the literature. Thus 2-amino-3-cyano-indene[2] and 1-amino-2-cyano-1-cyclopentene[6] were treated either with benzylamine or aniline to give *N*-benzyl- and *N*-phenyl compounds. Otherwise cyclic *N,N'*-dialkyl cyano enamines were accessible only by acylation of enamines with cyanogen chloride[3]. After partly unsuccessful attempts to alkylate compounds of type A at the nitrogen,

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[**] 2-Aminoindenes and their heterologs, Part 3.—Part 2: J. Pract. Chem., in press.

Table 1. *N,N*-Dialkyl cyano enamines *(1)*—*(3)* prepared by transamination. All compounds gave satisfactory elemental analyses.



(1) *(2)* *(3)*

Cpd.	R	R	R^1	Yield (%)	m.p. (°C) b.p. (°C/torr)	C≡N (IR) (cm^{-1})	N—C*H* (NMR, (δ)) (in $CDCl_3$)
(1a)	CH_3	CH_3		79	33 95—98/0.5	2180	3.10/s [b]
(1b)	$-CH_2CH_2OCH_2CH_2-$			44	145—148/1	2170	3.50/m
(1c)	$CH_2C_6H_5$	$CH_2C_6H_5$		63	175—180/10^{-3}	2170	4.50/s
(2a)	CH_3	CH_3	H	20 [a]	137	2190	3.05/s [c]
(2b)	$-CH_2CH_2OCH_2CH_2-$		H	47	176	2190	3.60/m
(2c)	$-CH_2CH_2OCH_2CH_2-$		CH_3, CH_3	≈100	223—225	2180	3.70/m
(3a)	CH_3	CH_3	CH_3	74 [a]	222	2180	3.15/s
(3b)	$-CH_2CH_2OCH_2CH_2-$		CH_3	90	223	2190	3.65/m
(3c)	$CH_2C_6H_5$	$CH_2C_6H_5$	$(CH_3)_3C$	80	196	2180	3.70/m

[a] Prepared *via* the cyano ketone.
[b] Coalescence at −87 °C.
[c] Coalescence at −23.2 °C; $\Delta G^{\neq} = 12.4$ kcal/mol.

the cyano enamines obtained on cyclization of dinitriles[4] were converted into *N,N*-dialkyl cyano enamines at elevated temperature and in the presence of small amounts of hydrochloride (see Table 1). Amines having high boiling points and the cyano enamines are refluxed with or without solvent; those having low boiling points are heated in autoclaves or bomb tubes.

The partial double bond character of the C—N bond in these cyano enamines is susceptible to quantitative analysis by low-temperature NMR spectroscopy[4].

1-Cyano-2-(N,N-dimethylamino)-1-cyclopentene (1a):

Dimethylamine (63 g, 1.4 mol) is passed into a solution of 1-amino-2-cyano-1-cyclopentene[5] (54 g, 0.5 mol) in dioxane (200 ml) and dimethylammonium chloride (1 g) is then added. The reaction mixture is heated to 165 °C for 24 h in an autoclave. After evaporation of the solvent, the product is vacuum distilled. Yield 54 g (79%) of *(1a)* as a colorless oil that solidifies at 33 °C.

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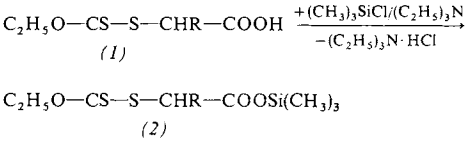
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1,3-Dithiolane-2,4-diones

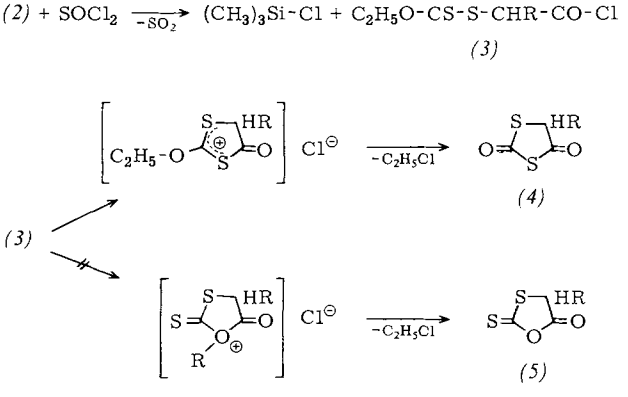
By *Hans R. Kricheldorf*[*]

The present communication describes the synthesis of the hitherto undescribed 1,3-dithiolane-2,4-diones *(4)*, R = H, CH_3, C_2H_5, which can be polymerized to polythiocarboxylic esters. The corresponding dioxolanediones also polymerize.

Reaction of sodium ethyl xanthate with 2-halo carboxylic acids yields the 2-(ethoxythiocarbonylthio)carboxylic acids *(1)*[1] which can be converted directly into the trimethylsilyl esters *(2)*. Compounds *(2)* can be distilled without decomposition.



Unlike the ethoxy compounds *(1)* and *(2)*, the corresponding methoxy compounds could not be isolated since they readily decompose with loss of COS. Reaction of the silyl esters *(2)* with thionyl chloride leads initially to the acyl chlorides *(3)* which cyclize at as low a temperature



R	*(2)* B.p. (°C/torr)	n_D^{20}	*(4)* B.p. (°C/torr)	n_D^{20}
a H	82—84/0.001	1.5110	68—70/0.1	1.6126
b CH_3	88—90/0.1	1.4985	53—55/0.1	1.5712
c C_2H_5	93—95/0.1	1.4920	64—66/0.5	1.5543

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as 25 °C with elimination of ethyl chloride to give the 1,3-dithiolane-2,4-diones *(4)*.

There is no evidence for the formation of the isomers *(5)*. Thus the IR spectrum of the reaction products *(4)* exhibits a carbonyl band in the region 5.9—6.0 μm (1700 to 1670 cm^{-1}) like the thiazolidine-2,5-diones[2,3], whereas a carbonyl band at 5.4 μm (1850 cm^{-1}) would be expected for *(5)*, as found in the case of 2-thioxo-5-oxazolidones (and the oxazolidine-2,5-diones)[3,4].

1,3-Dithiane-2,4-dione, a homolog of the title compounds, could not be synthesized since the precursor of type *(3)* [3-(ethoxythiocarbonylthio)propionyl chloride] is stable (b. p. 78—80 °C/0.01 torr, $n_D^{20} = 1.5535$).

The 1,3-dithiolane-2,4-diones *(4b)* and *(4c)* are yellow, highly refractive liquids that can be vacuum distilled below 100 °C. *(4a)* melts at 44—46 °C. In the presence of basic catalysts and on prolonged heating, particularly above 100 °C, they polymerize with elimination of COS:

$$n\,(4) \longrightarrow n\,COS + (-S-CHR-CO)_n$$

1,3-Dithiolane-2,4-dione (4) via trimethylsilyl 2-(ethoxythiocarbonylthio)carboxylate (2):

A solution of sodium ethyl xanthate (1 mol) in ethanol (500 ml) is mixed with a solution of halo carboxylic acid (1 mol) in 4 N aqueous sodium hydroxide (250 ml) and left to stand at 25 °C for 24 h. The solution is then filtered, evaporated down *in vacuo*, diluted to a volume of 500 ml with water, and acidified to pH 1 with concentrated hydrochloric acid. The precipitated carboxylic acid *(1)* is dissolved in methylene chloride and the solution is dried over Na_2SO_4 and concentrated by evaporation. The residual acid is dissolved in THF (1 liter) and silylated by dropwise addition of trimethylchlorosilane (*ca.* 1 mol) and triethylamine (1 mol). The mixture is diluted with light petroleum, filtered with exclusion of moisture, and the product *(2)* is then isolated from the filtrate by vacuum distillation; yield 70—80%.

A silyl ester *(2)* (0.5 mol) is added dropwise to a warm solution of pure thionyl chloride (90 g) in chloroform (250 ml). The resulting solution is heated until evolution of gas has ceased (1—2 h) and then evaporated down *in vacuo*. The product *(4)* is isolated by vacuum distillation, the bath temperature not being allowed rise over 100 °C; yield 60—70%.—Results of C, H analysis of the new products agree with the calculated values (±0.3%).

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Gram-Scale Purification of ^{244}Cm by Extraction Chromatography

By *K. Buijs, F. Maino, W. Müller, J. Reul*, and *Cl. Toussaint*[*]

Extraction chromatography, a technique combining the versatility of solvent extraction with the simplicity and good separation of chromatography, has been applied previously to the purification of mg-quantities of Cm[1,2].

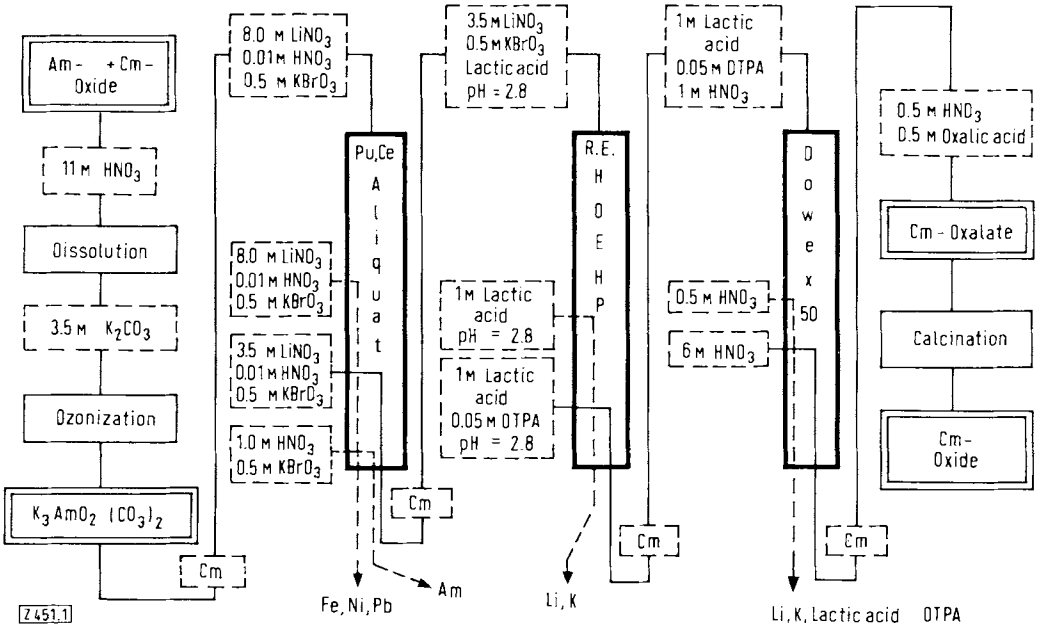


Fig. 1. Flowsheet for purification of ^{244}Cm by extraction chromatography.
R.E. = lanthanoids, DTPA = diethylenetriaminepentaacetic acid.

Extraction chromatography columns generally have a low specific capacity. The alpha-decay heat, which for ^{244}Cm corresponds to a thermal power of 2.83 W/g, therefore has less influence on the performance of extraction chromatography columns than on that of ion-exchange columns. Application of extraction chromatography to the purification of gram amounts of Cm was therefore thought feasible.

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An oxide mixture containing 5.9 g of ^{244}Cm and 5.1 g of ^{243}Am formed the starting material for the preparation of high-purity Cm oxide. A preliminary Am—Cm separation by two successive precipitations of $K_3AmO_2(CO_3)_2$ yielded a Cm fraction containing 2.7% of Am and an Am fraction containing 0.4% of Cm. The Cm fraction was then purified further by extraction chromatography and cation exchange as shown in the flowsheet (Fig. 1).

The whole purification process was carried out in nitrate medium which in comparison with chloride has the following advantages: less corrosion of glove-box equipment and less radiolytic decomposition of solutions. Furthermore, residual nitrate is decomposed during calcination of the oxalate.

Each of the extraction chromatography columns shown in the flowsheet had a volume of 1 liter and contained kieselgur as the inert supporting material. The weight ratios of tricaprylmethylammonium (Aliquat-336) nitrate and bis(2-ethylhexyl)phosphoric acid (HDEHP) to kieselgur were 0.25 and 0.11, respectively. During elution of the Cm fraction, the extraction chromatography columns were not affected by the passage of the solution of high power density, in contrast to the cation exchange column which, above the Cm-containing zone, was disturbed by gas bubbles. On all columns, the position of the Cm-fraction could be seen from the intense radioluminescence.

Analyses performed at Oak Ridge National Laboratory showed that the purification procedure reduced the inactive impurity content in the Cm from 7.8% to 0.65%; the residual Am content was 0.28%. The purification operation was carried out with master-slave manipulators in a glove-box which, for protection against neutrons from ^{244}Cm and gamma radiation from ^{243}Am (^{239}Np) and from traces of fission products, was installed behind a 25-cm shielding of water.

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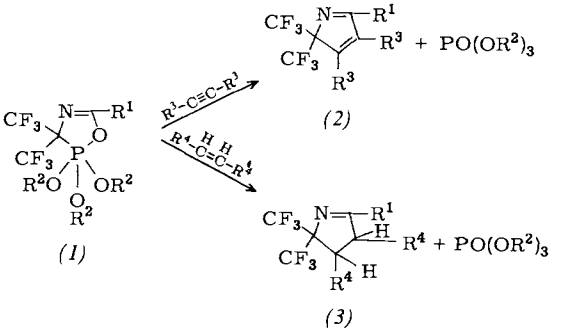
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Reactions of 4,5-Dihydro-1,3,5-oxazaphosph(v)oles with Alkynes and Alkenes[**]

By *Klaus Burger* and *Josef Fehn*[*]

4,5-Dihydro-1,3,5-oxazaphosph(v)oles *(1)*[1] react with alkynes and alkenes at temperatures between 100—140 °C in solvents such as toluene and xylene with elimination of phosphoric acid esters to yield 1:1 adducts. The products of this [3+2] cycloaddition are assigned the structures of 2*H*-pyrroles *(2)* and pyrrol-1-ines *(3)* on the basis of IR, NMR, and mass spectra data.

Similarly to the 1,3-dipolar addition of imidochlorides in the presence of triethylamine to double- and triple-bond systems, the reaction should proceed *via* nitrile ylides[2–4]. Recent studies provide compelling evidence for the intermediacy of nitrile ylides in the transformation of 4-acyl-5-oxazolones and 2-acyl-2*H*-5-oxazolones into trisubstituted oxazoles[5]; occurrence of nitrile ylides in 1,3-dipolar addition of 2,2-disubstituted 5-oxazolones has been proved by adduct formation[6].



(1) *(2)* *(3)*

Cpd.	*(1)*	Alkyne/alkene	M.p. (°C) b.p. (°C/torr)	Yield (%)	IR(cm^{-1})
(2a)	$R^1=C_6H_5$ $R^2=CH_3$	Dimethyl acetylene-dicarboxylate	97	70	1730, 1715 1615 [a]
(2b)	$R^1=C(CH_3)_3$ $R^2=C_2H_5$	Dimethyl acetylene-dicarboxylate	61	68	1730, 1618 [a]
(2c)	$R^1=C(CH_3)_3$ $R^2=CH_3$	Tolan	143	15	1615 [a]
(3a)	$R^1=C_6H_5$ $R^2=CH_3$	Dimethyl maleate	75	78	1730, 1615 [a]
		Dimethyl fumarate	75	75	1730, 1615 [a]
(3b)	$R^1=C(CH_3)_3$ $R^2=C_2H_5$	Dimethyl maleate	69/0.2	72	1735, 1620 [b]
	$R^1=C(CH_3)_3$ $R^2=CH_3$	Dimethyl fumarate	69/0.2	77	1735, 1620 [b]
(3c)	$R^1=CH(CH_3)_2$ $R^2=CH_3$	Dimethyl maleate	64/0.2	10	1720, 1625 [b]
(3d)	$R^1=C(CH_3)_3$ $R^2=CH_3$	Maleic anhydride	81–82	75	1860, 1785 1630 [a]

Recorded [a] in KBr, [b] as film with a Perkin-Elmar Infracord.

Owing to extremely ready epimerization, dimethyl maleate and fumarate give identical products on reaction with *(1)*. Methanolysis of *(3d)* also gives *(3b)* (*trans* form). All compounds give correct elemental analyses.

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2,2-Bis(trifluoromethyl)-3,4-bis(methoxycarbonyl)-5-phenyl-2H-pyrrole (2a):

2-Phenyl-4,4-bis(trifluoromethyl)-5,5,5-trimethoxy-4,5-dihydro-1,3,5-oxazaphosph(v)ole *(1)* (4.32 g, 11 mmol) was heated with dimethyl acetylenedicarboxylate in dry xylene for 10 h (bath temperature 125—135 °C). The solvent and the phosphoric acid ester formed during the reaction were removed by vacuum distillation and the residue crystallized on rubbing. It was recrystallized from a little methanol or methanol/water, yield 2.88 g (70%).

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[1] *K. Burger, J. Fehn,* and *E. Moll,* Chem. Ber. *104,* 1826 (1971).
[2] *R. Huisgen, H. Stangl, H. J. Sturm,* and *H. Wagenhofer,* Angew. Chem. *74,* 31 (1962); Angew. Chem. internat. Edit. *1,* 50 (1962).
[3] *R. Huisgen* and *R. Raab,* Tetrahedron Lett. *1966,* 649.
[4] *R. Huisgen,* Helv. Chim. Acta *50,* 2421 (1967).
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[6] *W. Steglich, G. Höfle,* and *P. Gruber,* to be published.

Orientation of Addition of Unsymmetrically Substituted Alkynes and Alkenes to 4,5-Dihydro-1,3,5-oxazaphosph(v)oles[**][1]

By *Klaus Burger* and *Josef Fehn*[*]

We recently reported on the reaction of 4,5-dihydro-1,3,5-oxazaphosph(v)oles *(1)*[2] with symmetrically substituted alkynes and alkenes leading to 2*H*-pyrroles and pyrrol-1-ines[1].

In all hitherto studied cases of the reaction of *(1)* and unsymmetrically substituted alkynes and alkenes both possible orientations were found. Table 1 lists isomeric ratios of compounds *(2)* or *(2')*:*(3)* and *(4)*:*(5)* respectively, as determined by NMR spectrometry, which were obtained in xylene at 120—140 °C (bath temperature). Examples for orientation in comparable reactions are given in ref. [3–6].

The mixtures *(2a)*/*(3a)*; *(2b)*/*(3b)*; *(2c)*/*(3c)*; and *(2d)*/*(3d)* obtained in the reaction *(1)*→*(2)*, *(3)* cannot be separated by distillation. Of the acids formed by alkaline hydrolysis and adjustment of the pH to 1—2, the β-keto acids derived from *(2)* undergo decarboxylation at room temperature[7]. Separation of *(6)* and *(7)* is now facile. The pyrrol-2-ine *(2'e)* is readily separable from *(3e)* by crystallization.

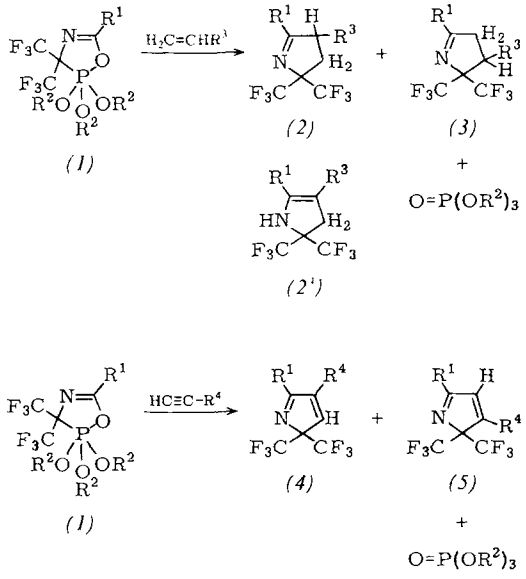


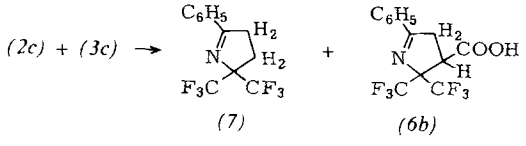
Table 1. Isomeric ratios.

	(1)	Alkene	*(2)* or *(2')*:*(3)*
(a)	$R^1=C(CH_3)_3$, $R^2=CH_3$	Methyl acrylate	*(2)* 65:35
(b)	$R^1=C(CH_3)_3$, $R^2=CH_3$	Ethyl acrylate	*(2)* 65:35
(c)	$R^1=C_6H_5$, $R^2=CH_3$	Methyl acrylate	*(2)* 68:32
(d)	$R^1=C_6H_5$, $R^2=CH_3$	Ethyl acrylate	*(2)* 63:37
(e)	$R^1=C(CH_3)_3$, $R^2=CH_3$	Acrylonitrile	*(2')* 80:20
		Alkyne	*(4)*:*(5)*
(f)	$R^1=C(CH_3)_3$, $R^2=CH_3$	Methyl propiolate	78:22
(g)	$R^1=C_6H_5$, $R^2=CH_3$	Methyl propiolate	70:30

Table 2. New compounds.

Cpd.	R^1	R^3 or R^4	M.p. (°C) b.p. (°C/torr)	Yield (%)	IR (cm^{-1})
(2'e)	$C(CH_3)_3$	CN	179	57	3175, 2185, 1600 [a]
(3a)	$C(CH_3)_3$	$COOCH_3$	96/12	95	1730, 1620 [b]
(3c)	C_6H_5	$COOCH_3$	99/0.3	90	1740, 1620 [b]
(3e)	$C(CH_3)_3$	CN	47–48	15	2230, 1630 [a]
(5f)	$C(CH_3)_3$	$COOCH_3$	98/12	80	1735, 1620 [c]
(6a)	$C(CH_3)_3$	COOH	162–163	95	3100–2750, 1710, 1620 [a]
(6b)	C_6H_5	COOH	134	90	3125–2700, 1715, 1615 [a]
(7)	C_6H_5	H	66	85	1610 [a]

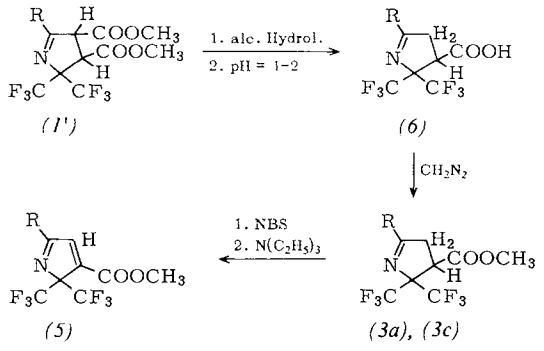
Recorded [a] in KBr, [b] as film, [c] in $CHCl_3$ with a Perkin-Elmer Infracord.



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(3a) and *(3c)* or *(5f)* formed as minor products on reaction *(1)* with methyl acrylate or methyl propiolate were synthesized isomer-free from the diester *(1')* and characterized.



(1') *(6)* *(5)* *(3a), (3c)*

The data for the compounds prepared are summarized in Table 2.

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Conformational Studies by Low Temperature ^{13}C-NMR Spectroscopy

By *Hans-Jörg Schneider, Roger Price*, and *Toni Keller*[*]

Low temperature ^{13}C-NMR spectra can be used to study chemical exchange processes in systems whose ^{1}H-NMR spectra are complicated by small shift differences and by coupling phenomena. The widely varying ^{13}C Larmor frequencies provide a wealth of information about the structure of the molecules concerned and about the energetics of their interconversions and permit measurement over a wide range of temperature; analysis is facilitated by the sole appearance of singlets in the ^{1}H-noise decoupled spectrum.

On inversion of *cis*-1,2-dimethylcyclohexane *(1)* into a chair conformation of equal energy the methyl groups change between equatorial and axial positions, causing all the C atoms to adopt corresponding stereoisomeric positions. This exchange process could be followed from the "frozen" equilibrium at 160°K to room temperature by pulse Fourier transform ^{13}C spectroscopy (see Fig. 1). The observed half-widths ranged from 87 Hz near the poorly defined coalescence point to about 0.5 Hz at 300°K; the limit of resolution is determined by the capacity of the computer storage. Evaluation of signal widths and, insofar as possible, of line separations too, of the 8 or 4 signals in the temperature range 200 to 270°K gave $\Delta H^{\neq} = 12 \pm 1$ kcal/mol, $\Delta G^{\neq}_{220} = 9.9$ kcal/mol. Analogous measurements on *cis*-1,4-dimethylcyclohexane *(2)* yielded $\Delta G^{\neq}_{220} = 9.3$ kcal/mol for the ring inversion barrier. These $\Delta G^{\neq}$ values agree to within an experimental accuracy of ± 0.5 kcal/mol with the inversion energies of cyclohexane and of 1,1-dimethylcyclohexane[1] determined by ^{1}H-NMR. The fact that substituents raise the inversion barrier by only a slight amount [compare *(1)* and *(2)* in particular] can be explained by ring deformation[1] or, alternatively, by a ground state of higher energy; moreover, the energy required is partly determined by the opening of the C—C angle which is affected only slightly by substituents.

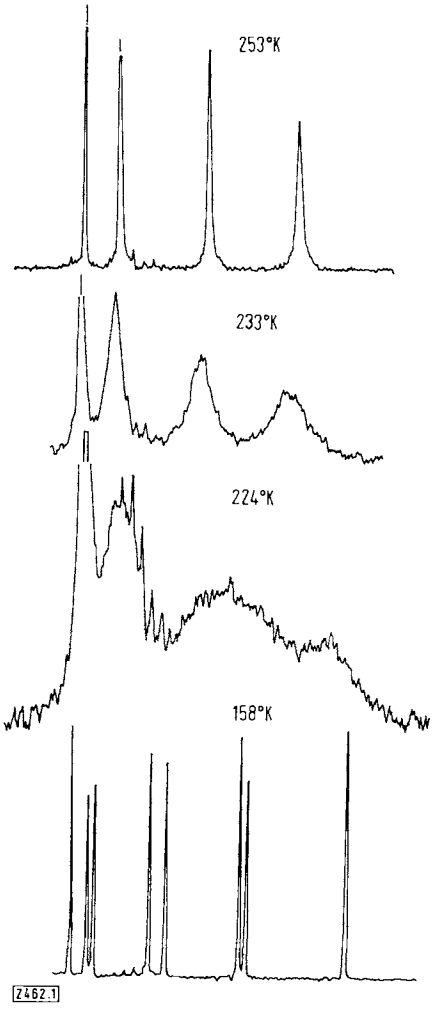


Fig. 1. ^{13}C-NMR spectra of *(1)* at different temperatures, measured in CCl_2F_2 + TMS (5:1) using $(CD_3)_2CO$ as lock.

The signals of *(1)* and *(2)* could be assigned unequivocally by their multiplicity in the off-resonance decoupled low-temperature spectrum and by application of known substituent rules[2, 3]. Comparison with the shifts calculated according to *Grant*[2] [see Figure 2] shows that the empirical shift parameters obtained from model substances will have to be corrected by the measurements on isolated conformers that have now become possible. The ^{13}C signal of an axial methyl is 5.9 ppm higher than that of an equatorial methyl group [see *(2)*, cf. [4]]. The upfield shift of a ^{13}C signal by γ substituents (by the diaxial γ protons in the case of an axial methyl group) must arise from both steric[2] and electronic effects[5, 6]. The difference in bonding between an axial and an equatorial methyl group is also

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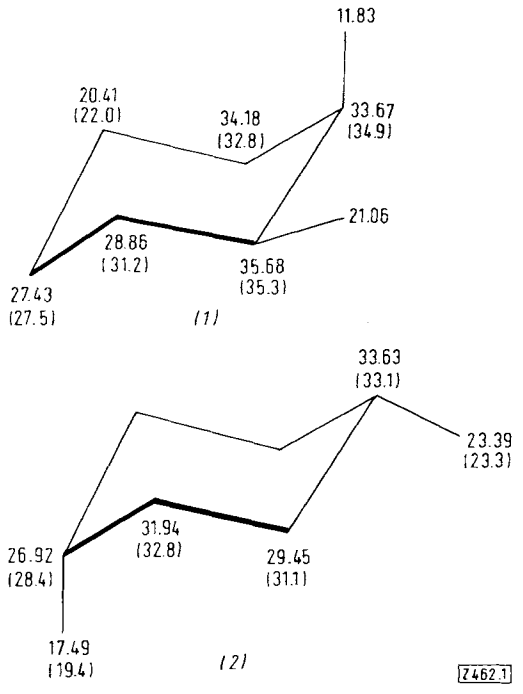


Fig. 2. ^{13}C-NMR shifts of *cis*-1,2-dimethylcyclohexane *(1)* at 158 °K and *cis*-1,4-dimethylcyclohexane *(2)* at 180 °K; solvent CCl_2F_2 + TMS (5:1). δ values in ppm downfield from TMS; values in parentheses shifts calculated according to *Grant* [2].

apparent from the diamagnetic shift of +5.7 ppm (resulting from mutual interaction of both groups in *(1)*) in the case of the axial group and of only +2.3 ppm for the equatorial group.

Identification of energetically unequal conformers and determination of their equilibria is facilitated by ^{13}C low-temperature spectroscopy[4]. The methyl signals of *cis*-4-methylcyclohexanol at 200 °K gave an equilibrium containing 7.7% with axial CH_3. The resulting energy difference of the conformers is $\Delta G = 1.07$ kcal/mol; this agrees with the value $\Delta G = 1$ kcal/mol obtained by addition of the conformational energies of CH_3 and OH groups, which indicates that the groups separated in the molecule exert no mutual interactions. This is confirmed by the shifts of the methyl group which, at $\delta_{TMS} = 23.5$ ppm or $\delta_{TMS} = 17.6$ ppm, do not differ from the values obtained for *cis*-1,4-dimethylcyclohexane *(2)* and for methylcyclohexane[4]. When evaluating ^{13}C-NMR spectra it should be borne in mind that the signal intensities can be falsified by differing relaxation times and Overhauser effects. That the relative abundances are correctly reproduced for identically substituted C atoms is shown, *e.g.*, by integration of the low-temperature spectrum of *(2)* to give area integrals for stereoisomeric (exchanging) C atoms having deviations of less than 0.5% for CH_3 and CH_2 and 4% for CH.

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revised: July 9, 1971 [Z 462 IE]
German version: Angew. Chem. *83*, 759 (1971)

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Elimination Reactions of Trichlorobutyl Acetates

By *Günther Maahs, Lutz Rohrschneider, Peter-Jürgen Frenzel,* and *Günter Peitscher*[*]

Dedicated to Professor Franz Broich on the occasion of his 65th birthday

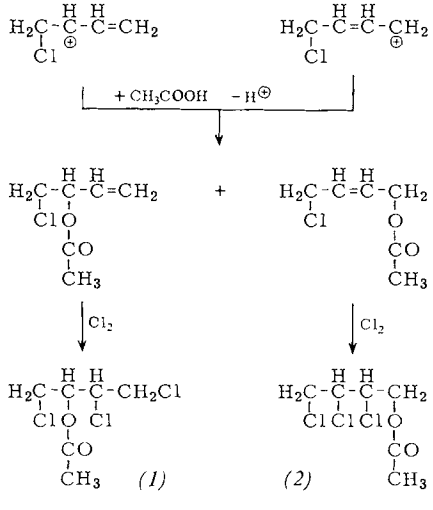
While the formation of chlorohydrin ethers and esters of monoolefins has been studied extensively[1], corresponding investigations on diolefins have received little attention[2]. In particular, reaction of diolefins and chlorine in the molar ratio 1:2 yields a rather complicated mixture of addition and substitution products. We have prepared trichlorobutyl acetates (chlorohydrinacetates of butadiene) and elucidated their elimination reactions.

Table 1. Results of combined GC/MS analysis (Perkin-Elmer Fractometer F 6/MAT mass spectrometer CH 4).

Peak No.	Overall ret. time (min)	Peak area (%)	Rel. intensities (%) *m/e* 43	49	61	73	169
1	10.9	9.1	100	2.8	3.1	0.2	0.5
2	11.3	52.3	100	2.6	2.9	0.2	0.7
3	11.9	15.1	100	3.1	5.1	16.2	0.02
4	13.3	23.5	100	2.9	3.8	18.7	0.01

Chlorine is passed into a solution of butadiene in glacial acetic acid (molar ratio $C_4H_6:Cl_2 = 1:2$) in the dark at 15—18 °C in the presence of traces of oxygen. (Alternatively, butadiene and chlorine can be passed simultaneously into glacial acetic acid.) Distillation at 75—78 °C/3 torr (116 to 120 °C/11 torr) gave a fraction (yield 25—35%; $n_D^{20} = 1.4783$) that could be separated into four components on a 50-m polyphenyl ether capillary column at 175 °C. Relevant GC/MS data are listed in Table 1.

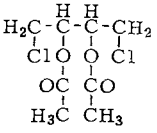
According to Table 1, components 1 and 2 and 3 and 4 appear to be very similar in the mass spectra, although the two groups may readily be distinguished. The large proportion of fragments having mass number 73 ($-CH_2OCOCH_3$) in components 3 and 4 suggests the presence of the 1-acetate *(2)* since the 2-acetate cannot possibly give this fragment. Thus the reaction product consists of 61% of the trichloro-



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sec-butyl acetate [(1-chloromethyl-2,3-dichloropropyl) acetate] *(1)* and 39% of the trichloro-*n*-butyl acetate [2,3,4-trichlorobutyl acetate] *(2)* which are both composed of two diastereomers.

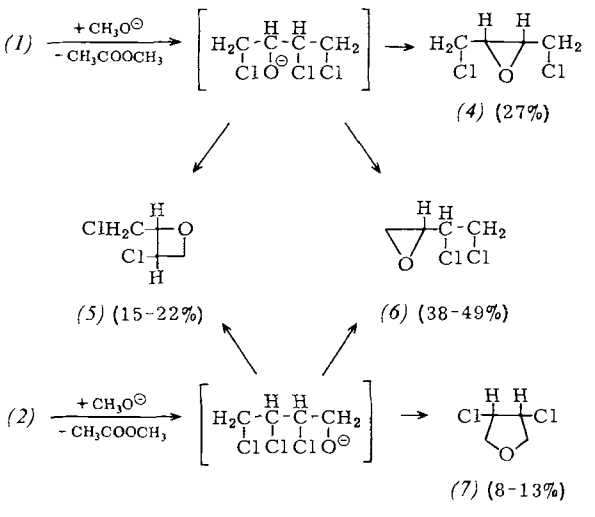
The other distillation fractions were not studied. A white solid crystallized from the high-boiling constituents (m.p.



(3)

115—116 °C from methylcyclohexane) which has the structure *(3)* according to its NMR and mass spectra.

The mixture of *(1)* and *(2)* was then treated in methanolic solution with an equimolar amount of sodium methoxide at room temperature. After the NaCl had been filtered off



and the solvent pumped off, the residue was distilled at 57—70 °C/10 torr (yield 60%, $n_D^{20} = 1.4790$).

The product was separated into four components on a preparative scale by gas chromatography. According to the mass spectrum, the components are isomers of composition $C_4H_6OCl_2$. The four cyclic structures *(4)*—*(7)* were assigned on the basis of the NMR and IR spectra. The methanol removed from the reaction mixture was also found to contain an equimolar amount of methyl acetate with respect to the product.

The nucleophilic substitution therefore seems to lead to an intramolecular elimination with ring closure. [The figures in parentheses represent the limiting percentages of product found for a variety of experimental conditions (reaction time 10—120 min, reaction temperature 20—65 °C, use of methanolic potassium hydroxide).]

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[1] *Houben-Weyl-Müller*: Methoden der Organischen Chemie. 4th Edit. G. Thieme Verlag, Stuttgart 1962, Vol. V/3, pp. 775ff.

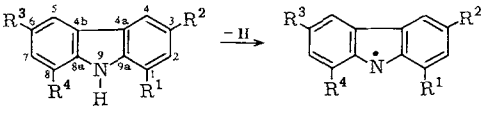
[2] See, *e.g.*, *W. Groshnik* and *R. A. Mallory*, J. Amer. Chem. Soc. *72*, 4610 (1950).

1,3,6,8-Tetra-*tert*-butyl-9-carbazyl: A Crystalline Monomeric Aminyl Radical[1][**]

By *Franz A. Neugebauer* and *Hans Fischer*[*]

Direct linkage of two *ortho* positions in diphenylaminyl gives the 9-carbazyl system, a planar aminyl. In order to determine the properties of 9-carbazyl radicals we have synthesized the *tert*-butyl substituted carbazoles *(1a)* to *(1d)* and dehydrogenated them to give the 9-carbazyl radicals *(2a)*—*(2d)*.

Reaction of carbazole (1 mol) with *tert*-butyl chloride (6 mol) and $AlCl_3$ (1 mol) at room temperature gives 1,3,6,8-tetra-*tert*-butylcarbazole *(1a)* (m.p. 191—192 °C, 72%), 1,3,6-tri-*tert*-butylcarbazole *(1d)* (m.p. 136—137 °C, 5%), and 3,6-di-*tert*-butylcarbazole (m.p. 228—229 °C, 10%)[2, 3]. 1,8-Di-*tert*-butylcarbazole *(1b)* (m.p. 173—174 °C) is obtained from *(1a)* *via* 3,6-dinitro- (m.p. 289—290 °C), 3,6-diamino- (m.p. 254—255 °C), and 3,6-diiodo-1,8-di-*tert*-butylcarbazole (m.p. 230—231 °C)[3]. 1,3,8-Tri-*tert*-butylcarbazole *(1c)* (m.p. 131—132 °C) can be prepared similarly from *(1a)* by way of 3-nitro- (m.p. 227—228 °C),



(1) *(2)*

(a), $R^1 = R^2 = R^3 = R^4 = C(CH_3)_3$
(b), $R^1 = R^4 = C(CH_3)_3$; $R^2 = R^3 = H$
(c), $R^1 = R^2 = R^4 = C(CH_3)_3$; $R^3 = H$
(d), $R^1 = R^2 = R^3 = C(CH_3)_3$; $R^4 = H$

3-amino- (m.p. 159—160 °C), and 3-iodo-1,6,8-tri-*tert*-butylcarbazole (m.p. 135—136 °C)[3].

Addition of an equivalent of iodine oxidizes a solution of the lithium salt of *(1a)* in benzene to the deep blue (benzene: $\lambda_{max} = 660$ nm, $\log \varepsilon = 4.02$) species 1,3,6,8-tetra-*tert*-butyl-9-carbazyl *(2a)* which forms blue-black crystals (dec. p. 144—145 °C) from light petroleum. Hydrogenation of *(2a)* with $Pd/BaSO_4$ in pyridine indicates a radical content of 92%. The extremely strong ν(NH) band of the carbazole *(1a)* at 3520 cm^{-1} is just detectable in the IR spectrum of the radical *(2a)*. Oxidation of the carbazoles *(1b)*—*(1d)* with lead dioxide in benzene also gives blue 9-carbazyl

Table 1. Coupling constants and spin densities for 9-carbazyl.

Position	Exp. [a] $\lvert a_i[G]\rvert$	Exp. [a] $\lvert\rho_i^\pi\rvert$	Calc. [4] [b] ρ_i^π
1	3.8	0.16	0.189
2	0.9	0.038	−0.053
3	4.3	0.18	0.152
4	0.15	0.006	0.023
4a	—	—	0.073
9	6.9	0.24	0.284
9a	—	—	−0.026

[a] $a^H = -23.7\,\rho_C$ [5]; $a^N = 28.6\,\rho_N$ [6].

[b] $\beta_{CN} = 1.2\,\beta_{CC}$; $\beta_{C-4aC-4b} = 0.8\,\beta_{CC}$; $\alpha_N = \alpha_C + 1.2\,\beta_{CC}$; $\lambda = 1.2$.

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radicals which, however, are less stable and have not yet been isolated.

The carbazyls *(2a)*—*(2d)* give well resolved ESR spectra, *e.g.*, *(2a)* in benzene: $g=2.0033$; $a^{N}=6.86$, $a^{H_{2,7}}=0.93$, $a^{H}R^{2}$, $R^{3}=0.175$, $a^{H_{4,5}}=0.175$ G; *(2b)* in benzene: $a^{N}=6.97$, $a^{H_{2,7}}=0.89$, $a^{H_{3,6}}=4.3$, $a^{H_{4,5}}=0.14$ G. The ESR coupling constants show that the unpaired electron is largely delocalized over the planar π system. The experimental values found for the carbazyl derivatives *(2a)* to *(2d)* are in good agreement with the calculated spin densities for 9-carbazyl (Table 1). However, the sign of the calculated spin density in position 4 (sign of corresponding H coupling) still has to be determined experimentally (NMR).

The exceptional stability of the carbazyl *(2a)* stems from the steric shielding of the reactive aminyl nitrogen N-9 and the reactive positions C-1 and C-3 by the bulky *tert*-butyl substituents.

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Addition of Acrylonitrile to Derivatives of 1,4-Dihydropyridine

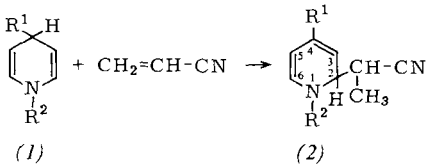
By *Reinhard A. Sulzbach* and *Abul F. M. Iqbal*[*]

The 1,4-dihydropyridine system has hitherto attracted attention mainly because of its role as an intermediate in hydrogen transfer by pyridine nucleotides[1, 2]. The reactions carried out with 1,4-dihydropyridine compounds are limited to just a few examples[3–6].

We have now found that 1,4-dihydropyridines of type *(1)* undergo a surprising kind of reaction with acrylonitrile to give the 2-substituted 1,2-dihydropyridines *(2)*.

If the reaction is carried out with a molar excess of acrylonitrile, the Diels-Alder adduct of *(2)* and acrylonitrile can be isolated.

1,4-Dihydroquinolines react similarly with acrylonitrile to give 2-substituted 1,2-dihydroquinolines, as could be demonstrated in the case of 1,4-bis(trimethylsilyl)-1,4-dihydroquinoline.



(1) *(2)*

(a), $R^{1}=R^{2}=$ trimethylsilyl
(b), $R^{1}=H$, $R^{2}=$ 2,6-dichlorobenzyl
(c), $R^{1}=H$, $R^{2}=$ phenyl

In order that reaction may occur between a 1,4-dihydropyridine and acrylonitrile, an H atom must be present on C-4 of the dihydropyridine ring. After ten days' heating of 4-methyl-1,4-bis(trimethylsilyl)-1,4-dihydropyridine and acrylonitrile to 100 °C only unreacted starting material could be isolated. The 1,4-dihydropyridine system therefore shows no tendency to undergo reactions that are typical of enamines[7]. This observation is in accord with earlier findings that 1,4-dihydropyridines cannot be made to react with alkyl iodides in the manner expected for enamines[5, 6].

2-(1-Cyanoethyl)-1,4-bis(trimethylsilyl)-1,2-dihydropyridine (2a):

Acrylonitrile (5.3 g, 0.1 mol) is added slowly to 1,4-bis(trimethylsilyl)-1,4-dihydropyridine[8] (22.6 g, 0.1 mol) under argon in a 50-ml two-necked flask (thermometer, dropping funnel, magnetic stirrer). After 24 hours' reaction at room temperature, distillation gave *(2a)* (17 g, 61%) as a yellowish-green oil, b.p. 78 °C/10^{-3} torr; ^{1}H-NMR (C_6D_6): $\tau=6.38$ (H-2); 4.35 (H-3); 4.57 (H-5); 4.06 (H-6); 7.40; 9.18 (CH_3); 9.84 ($(CH_3)_3SiC$); 10.07 ($(CH_3)_3SiN$); $J_{2,7}=8.4$ Hz; $J_{3,2}=5.8$ Hz; $J_{3,5}=1.19$ Hz; $J_{6,5}=6.7$ Hz; $J_{6,2}=1.1$ Hz; $J_{7,8}=7.3$ Hz; M.W. (Simon/Tomlinson) = 277; correct elemental analyses.

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Diethylaminotetrafluorophosphorane by Fluorolytic Cleavage of the P=N Bond[**]

By *Manfred Bermann* and *John R. Van Wazer*[*]

Phenyliminodiethylaminophosphorus(v) dichloride *(1)*[1] and an excess of antimony trifluoride do not give phenyliminodiethylaminophosphorus(v) difluoride but react further with splitting of the P=N bond to yield diethylaminotetrafluorophosphorane *(2)*[2].

$$\underset{(1)}{C_6H_5N{=}PN(C_2H_5)_2Cl_2} + SbF_3\ (\text{in excess}) \rightarrow \underset{(2)}{(C_2H_5)_2NPF_4} + SbCl_3 + Sb + \textit{by-products}$$

This behavior is unexpected, as the P=N bond in phenyliminodialkylaminophosphorus(v) dichlorides is usually quite inert. Thus, in general, HCl may not be added direct-

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ly[3] but only by the way of an ammonolysis[4], methyl iodide adds only slowly[5], and hydrolysis to the anilino group[6] also proceeds gradually. However, fluorolytic cleavage of the P=N bond is known for some phosphazo trichlorides: $RN{=}PCl_3$ ($R = F_2OP$[7], $ClSO_2$[8,9], FSO_2[7,10,11], CF_3SO_2[12], perfluoroalkyl-CO[13]).

The procedure described herein for the synthesis of diethylaminotetrafluorophosphorane *(2)* is carried out in three steps from commercially available reagents

$$2\,C_6H_5NH_2 + 2\,PCl_5 \rightarrow (C_6H_5N{=}PCl_3)_2$$

$$(C_6H_5N{=}PCl_3)_2 \rightarrow 2\,C_6H_5N{=}PN(C_2H_5)_2Cl_2 \quad (1)$$

$$2\,C_6H_5N{=}PN(C_2H_5)_2Cl_2 \rightarrow 2\,(C_2H_5)_2NPF_4 \quad (1) \quad (2)$$

This synthesis avoids the unpleasant and expensive utilization of PF_5 as in the case of the silazane cleavage of $(C_2H_5)_2NSi(CH_3)_3$[14] or the thermolytic decomposition of the adduct $(C_2H_5)_2NH \cdot PF_5$[15]. The compound $(C_2H_5)_2NPF_4$ cannot be obtained by fluorination of $(C_2H_5)_2NPCl_2$ with SbF_3[16].

Diethylaminotetrafluorophosphorane (2)

Finely ground SbF_3 (12 g) is added to *(1)* (13.5 g) (exothermic!) and the flask is immediately mounted on a distillation apparatus flushed with nitrogen. Distillation at 100—102 °C/756 torr (lit.[14] = 99—100 °C/760 torr) gives compound *(2)* (5.2 g, 59%) as a clear liquid. NMR spectra[17]: $\tau = 7.07$ (CH_2), 9.00 (CH_3), $J_{HH} = 7.3$ Hz, $J_{PNCH_2} = 2.0$ Hz; $\delta = +68.7$ ppm (P), $\delta = +65.1$ ppm (F), $J_{PF} = 859$ Hz [from ^{31}P-NMR], 853 Hz [from ^{19}F-NMR] (lit.[14,18]: +70.2 ppm, +66.5 ppm; 851, 863 Hz). $SbCl_3$ (3.4 g) is obtained on further distillation at 224—228 °C. The green-black residue contains elemental antimony as well as products which were not further characterized.

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P,P-Diphenylethylenediphosphane[**]

By *R. B. King* and *Pramesh N. Kapoor*[*]

This communication reports the preparation of *P,P*-diphenylethylenediphosphane *(4)*, apparently the first known compound incorporating both the primary phosphane and tertiary phosphane functional groups. The synthesis of *(4)* provides the first example of the synthesis of a PCH_2CH_2P unit by the base-catalyzed addition of a phosphorus-hydrogen bond across the carbon-carbon double bond of a vinyl group bonded to a *four-coordinate* phosphorus atom. All previously reported[1,2] syntheses of this kind employed derivatives with vinyl groups bonded to *three-coordinate* phosphorus atoms.

$$H_2C{=}CH{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2 + (C_6H_5)_2PH \rightarrow$$
(1) *(2)*

$$\left[(C_6H_5)_2P{-}CH_2{-}CH_2{-}\overset{\overset{O}{\|}}{P}(OC_2H_5)_2\right] \rightarrow$$
(3)

$$(C_6H_5)_2P{-}CH_2{-}CH_2{-}PH_2$$
(4)

$$P(CH_2{-}CH_2{-}P(C_6H_5)_2)_3 \quad (5)$$

A mixture of equimolar quantities of diethyl vinylphosphonate *(1)*[3] and diphenylphosphane *(2)* in tetrahydrofuran solution was boiled under reflux for 20 h in the presence of ≈5% potassium *tert*-butoxide catalyst. After cooling to room temperature the tetrahydrofuran and unreacted starting materials were removed by distillation up to 140 °C/0.8 torr. A non-crystalline viscous pasty residue remained which was presumably the expected adduct *(3)* but could not be purified by either crystallization or vacuum distillation. This residue was dissolved in tetrahydrofuran and reduced with a solution of $LiAlH_4$ in diethyl ether in the usual manner. After the reduction was complete, the reaction mixture was hydrolyzed cautiously with 6 N aqueous hydrochloric acid. The ether layer was separated, dried over anhydrous sodium sulfate, and distilled to give, after removal of the diethyl ether, a 21% yield of colorless very air-sensitive (sometimes pyrophoric) liquid *(4)*, b. p. 151—152 °C/0.5 torr. C, H analysis gave correct values.

The infrared spectrum (liquid film) exhibits a medium intensity ν(PH) frequency at 2294 cm^{-1}. The ^{1}H-NMR spectrum (neat liquid) shows a doublet of triplets ($J \approx 7$ Hz) centered at τ 7.35 arising from the PH_2 group, multiplets

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[17] ^{1}H-NMR spectrum *vs.* external TMS (Varian A-60); ^{19}F- and ^{31}P-NMR spectra as neat liquids *vs.* $CFCl_3$ and 85% H_3PO_4, both external, respectively (Varian XL-100-15); sample temperature: 29 °C.

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centered at τ 7.87 and $\tau \approx 8.5$ arising from the two non-equivalent CH_2 groups, and multiplets around τ 2.65 and $\tau \approx 2.9$ arising from the phenyl groups. The ^{31}P-NMR spectrum (neat liquid) exhibits a singlet and a triplet ($J = 185$ Hz) arising from the tertiary phosphorus atom and the primary phosphorus atom, respectively, thereby providing unambiguous demonstration of structure *(4)*. The mass spectrum (70 eV) exhibits in addition to the molecular ion (*m/e* 246) the major fragment ions $(C_6H_5)_2PPH_2^{\oplus}$ (*m/e* 218), $(C_6H_5)_2PCH_2CH_2^{\oplus}$ (*m/e* 213), $(C_6H_5)_2PCH_2^{\oplus}$ (*m/e* 199), $(C_6H_5)_2P^{\oplus}$ (*m/e* 185), $C_{12}H_8P^{\oplus}$ (*m/e* 183), and $C_6H_5P^{\oplus}$ (*m/e* 108). Fragmentation processes supported by observed metastable ions include C_2H_4 elimination from the molecular ion and phosphorus elimination from $C_{12}H_8P^{\oplus}$

The compound *(4)* has two phosphorus-hydrogen bonds and thus should undergo base-catalyzed additions to appropriate unsaturated compounds. Reaction of *(4)* with two equivalents of diphenylvinylphosphane for 20 h in boiling tetrahydrofuran in the presence of potassium *tert*-butoxide catalyst gave an 84% yield of the known[1,2] tripod tetratertiary phosphane *(5)*, m.p. 129—130 °C (lit.[2] m.p. 131 °C) identified by its infrared spectrum in the 4000—600 cm^{-1} region. This conversion of *(4)* into *(5)* provides an unambiguous chemical demonstration of the structure of *(4)*.

Similar reaction sequences should be useful for converting $C_6H_5PH_2$ into $C_6H_5P(CH_2CH_2PH_2)_2$ and PH_3 into $P(CH_2CH_2PH_2)_3$. These compounds should in turn open up possible routes to new polytertiary phosphanes with PCH_2CH_2P units which are not accessible by previously developed techniques[1,2]. Unfortunately, the odor of *(4)* was so disagreeable, pervasive, and persistent that we have been forced to suspend our efforts to prepare the presumably still more malodorous derivatives $C_6H_5P(CH_2CH_2PH_2)_2$ and $P(CH_2CH_2PH_2)_3$.

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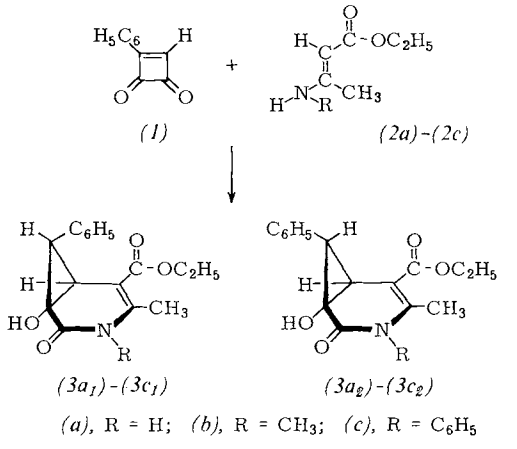
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Synthesis and Reactions of 1-Hydroxy-3-azabicyclo[4.1.0]hept-4-en-2-ones[1][**]

By *Walter Ried* and *Friedrich Bätz*[*]

Phenylcyclobutenedione and enamines react to afford substituted 3-hydroxy-2-pyridones *(4)*[2] by way of intermediates whose structure is elucidated below. The 1:1 adducts[2] obtained from phenylcyclobutenedione *(1)* and substituted 3-aminocrotonic esters *(2a)*—*(2c)* in benzene are found to be 1-hydroxy-4-methyl-2-oxo-7-phenyl-3-azabicyclo[4.1.0]hept-4-ene-5-carboxylic esters *(3a)* to *(3c)* of different configurations that are assigned by NMR spectroscopy.

IR spectra (KBr): *(3a)*, ν(OH) and/or ν(NH) = 3480, 3220, 3100, 2980 cm^{-1}, ν(CO) = 1700—1680 cm^{-1} (lactam and α,β-unsaturated ester); *(3b)* and *(3c)*, ν(OH) $\approx$ 3300 cm^{-1}, ν(C=O) = 1720 and ~1650 cm^{-1}. ^{1}H-NMR spectra (cf. Table): *(3a)* (in $CDCl_3$ and [D_6]-DMSO, TMS internal): an AB system with $\tau_A = 7.09$ and $\tau_B = 8.01$ ppm ($J_{AB} = 6.3$ Hz) occurs as well as the expected signals; *(3b)* (in $CDCl_3$ with a somewhat larger amount of hexamethyldisiloxane (HMDSO) as standard) gives a weakly split AB system (2H) ($J_{AB} = 10.2$ Hz); *(3c)* (in $CDCl_3$ against TMS) gives a weakly split AB system around $\tau_{AB} = 6.82$ ppm ($\tau_A = 6.76$, $\tau_B = 6.88$ ppm, calculated values), ($J_{AB} = 10.2$ Hz).



(a), R = H; *(b)*, R = CH_3; *(c)*, R = C_6H_5

The configurations can be determined from the coupling constants. According to these, *(3a)* exists as *(3a$_2$)* ($J_{trans} = 5$—7 Hz[3]), *(3b)* and *(3c)* exist as *(3b$_1$)* and *(3c$_1$)*, respectively ($J_{cis} = 9$—11 Hz[3]). (*cis* and *trans* refer to the arrangement of the H atoms on the cyclopropane ring.)

(3b$_2$) can be isolated as well as *(3a$_2$)*, *(3b$_1$)*, and *(3c$_1$)*. It can be obtained in about 2% yield from the mother liquor from the batch of *(3b$_1$)* by chromatographic separation on silica gel with methylene chloride as eluant. *(3b$_2$)* is obtained in *ca.* 25% yield if the reaction of *(1)* with *(2b)* is effected in dioxane saturated with dry HCl.

Comparison of the ^{1}H-NMR spectra of *(3a$_2$)*, *(3b$_2$)*, and *(3b$_1$)* can be regarded as further proof of the structures assigned (cf. Table). For *(3a$_2$)* the signal e' for the *endo*-proton appears at relatively high field strength because of ring current effects (cf. the ^{1}H-NMR spectrum of 2,5-diphenyl-3,4-diazanorcaradiene[4]). The signals e and e' of

Table. Comparison of the ^{1}H-NMR spectra of *(3a$_2$)*, *(3b$_2$)*, and *(3b$_1$)* (τ values in ppm against TMS).

Signal	*(3a$_2$)*	*(3b$_2$)*	*(3b$_1$)*	Number of H	Assignment
a	2.6–2.85	2.6–2.9	2.65–3.15	5	C_6H_5
b	3.59	6.45	4.29	1	OH
c	5.82	5.79	5.68	2	O—CH_2—CH_3
d	—	6.75	7.26	3	N—CH_3
e	7.09	6.84	6.85	1	CH—CH—C_6H_5
f	7.74	7.53	8.00	3	C—CH_3
e'	8.01	8.04	6.85	1	CH—CH—C_6H_5
g	8.72	8.69	8.62	3	O—CH_2—CH_3

(3a$_2$) and *(3b$_2$)* appear at approximately equal field strength. However, with *(3b$_1$)* the signals assigned to the C_{ring}-CH_3 and N—CH_3 group, respectively, are shifted by ring current effects from the corresponding signals of *(3b$_2$)*.

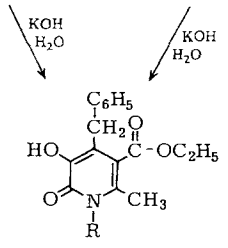
If treated with aqueous alkali hydroxides, the compounds *(3a$_2$)*, *(3b$_2$)*, *(3b$_1$)*, and *(3c$_1$)* rearrange to the substituted

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[**] Reactions of Cyclobutenediones, Part 22.—Part 21: *W. Ried* and *H. Kohl*, Chem. Ber., in press.

3-hydroxy-2-pyridones *(4)*[2]. Formation of the compounds *(4)* from the bicyclics *(3)* may occur analogously to the base-catalyzed ring opening of cyclopropanols[5].

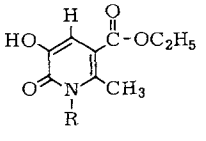
(3b₁), (3c₁) *(3a₂), (3b₂)*



(4a)-(4c)

On catalytic hydrogenation in presence of platinum, *(3b₁)* and *(3c₁)* absorb 4 molar proportions of hydrogen, affording 3-hydroxy-2-pyridones *(5b)* and *(5c)*, respectively; *(5b)*, m.p. 162—163 °C, yield ≈50%; *(5c)*, m.p. 184 to 185 °C, yield ≈40%. The NMR spectra, as well as the C=O stretching vibration bands at 1650 cm^{-1} (2-pyridone[6, 7]) serve as structural proof for *(4b)* and *(4c)*.

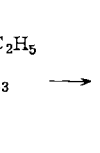
(3b₁) *(3c₁)* $\xrightarrow[[-C_7H_{14}]]{4\ H_2}$

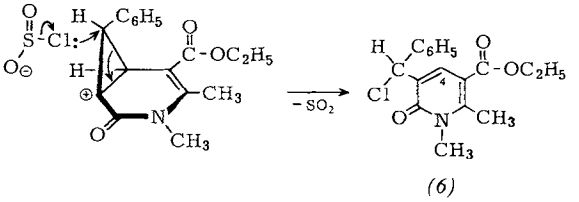


(5b), (5c)

Treating *(3b₁)* with thionyl chloride affords 3-(α-chlorobenzyl)-5-(ethoxycarbonyl)-1,6-dimethyl-2-pyridone *(6)*, whose formation may be explained as due to an S_Ni' type attack by the thionyl chloride. Conversion of similar bicyclics into 2-pyridones has been described[8].

(3b₁) $\xrightarrow[-HCl]{SOCl_2}$





(6)

The C=O stretching vibration band at 1640 cm^{-1} in the IR spectrum of *(6)* can be assigned to the 2-pyridone portion[6, 7]. The ^{1}H-NMR signal at $\tau = 1.96$ ppm (H-4) appears at low field, as does the corresponding signal of 3-benzyl-5-(ethoxycarbonyl)-1-methyl-6-phenyl-2-pyridone[9] because of anisotropy effects of the benzene nucleus and the ester-carbonyl group ($\tau = 2.15$ ppm).

Ethyl 1-hydroxy-3,4-dimethyl-2-oxo-7-phenyl-3-azabicyclo-[4.1.0]hept-4-ene-5-carboxylate (3b₂)

Gaseous HCl is passed to saturation into a solution of *(1)* (1.58 g, 0.01 mol) in dry dioxane (about 80 ml). After addition of *(2b)* (2.2 g, 0.15 mol), the mixture is stirred at 20 °C for 7 h, the hydrochloride formed is filtered off, and the solvent is removed in a rotary evaporator. By chromatographic separation on silica gel (Woelm 0.05—0.2 mm) with benzene/ethyl acetate (3:1) as eluant first a fore-fraction is obtained and then a fraction from which *(3b₂)* crystallizes on removal of the solvent; recrystallization from benzene/cyclohexane gives a *ca.* 25% yield of material, m.p. 128—129 °C.

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[1] Part of the Dissertation of *F. Bätz*, Frankfurt University 1970.

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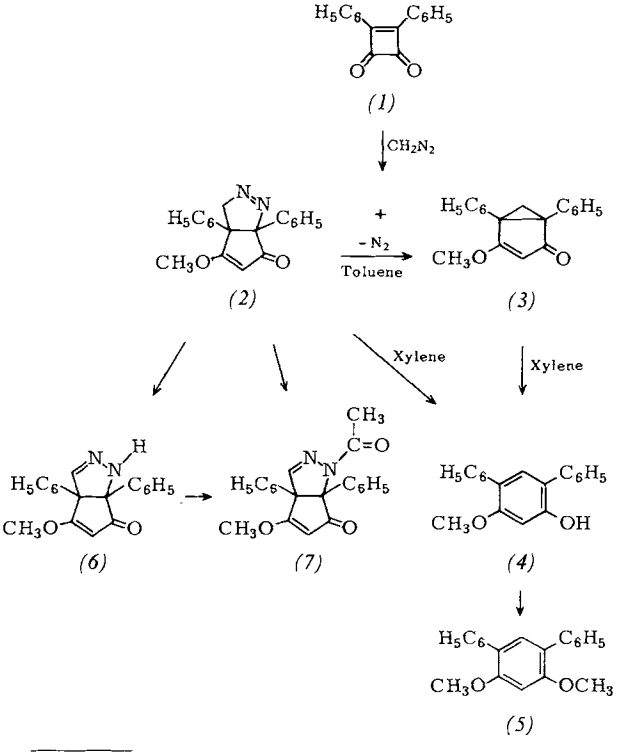
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Reaction of Diphenylcyclobutenedione with Diazomethane[**]

By *Walter Ried, Walter Kuhn*, and *Arthur H. Schmidt*[*]

Reaction of diazoalkanes with small unsaturated carbocycles (cyclopropenes[3], cyclobutenes[4]) has been studied



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[**] Reactions of Cyclobutenediones, Part 23.—Part 22: *W. Ried* and *F. Bätz*, Angew. Chem. *83*, 763 (1971); Angew. Chem. internat. Edit. *10*, 735 (1971).

previously in detail, but nothing has so far been reported about the action of diazoalkanes on cyclobutenediones.

On reaction of diphenylcyclobutenedione *(1)* with an excess of diazomethane we obtained almost equal yields of 3a,6a-dihydro-4-methoxy-3a,6a-diphenylcyclopentapyrazol-6(3*H*)-one *(2)* and 2-methoxy-1,5-diphenylbicyclo-[3.1.0]hex-2-en-4-one *(3)*, which can be separated by virtue of their differing solubilities in CCl_4. The properties of the new compounds are reported in the annexed Table.

observed, and since the reaction of cyclones with diazomethane requires an extremely long time[8], we exclude any reaction mechanism by way of a cyclone. Comparison with the reaction of diazomethane with 2,4,5-triphenyl-4-cyclopentene-1,3-dione[9], which leads immediately to 3-methoxy-2,4,5-triphenylcyclopentadien-1-one, shows that a cyclopentenedione also does not occur as intermediate. We thus assume that in the reaction described above a 1,3-dipolar addition of the diazomethane to the double bond of the cyclobutenedione first occurs and only

Table. Some properties of compounds *(2)*—*(7)*. Satisfactory elemental analyses and UV and mass spectra have been obtained.

Cpd.	m.p. (°C) (Solvent)	IR (cm^{-1})	NMR (τ, ppm)	Conditions
(2)	141 (dec) (CCl_4)	2940, 2850 (CH) 1690 (CO) 1600 (CC) 1550 (NN)	2.6–3.3 (10H/m) 4.0 (1H/s) 4.52, 4.73 (2H) J = 20 Hz 5.92 (3H/s)	60 MHz DMSO
(3)	168 (CH_3OH)	2960, 2860 (CH) 1690 (CO) 1610, 1590 (CC)	2.86, 2.9 (10H/d) 4.84 (1H/s) 6.2 (3H/s) 7.26, 7.83 (2H) J = 5 Hz	60 MHz DMSO
(4)	141–142 (Benzene/ Cyclohexane)	3410 (OH) 2980, 2940, 2850, 900 (CH) 1610 (CC)	2.4–3 (11H/m) 3.48 (1H/s) 5 (1H/br. s, D_2O-exchange) 6.32 (3H/s)	100 MHz $CDCl_3$
(5)	99–100 (CH_3OH)	2960, 2930, 2840, 900 (CH) 1610, 1580 (CC)	2.5–2.8 (10H/m) 3.48 (1H/s) 2.9 (1H/s) 6.26 (6H/s)	100 MHz $CDCl_3$
(6)	220–222 (dec) (CH_3OH)	3280 (NH) 2940, 2840 (CH) 1700 (CO) 1600 (CC)	2.77 (1H/s, D_2O-exchange) 2.9–3.45 (10H/m) 3.49 (1H/s) 4.18 (1H/s) 6.16 (3H/s)	100 MHz [D_6]-Acetone
(7)	229–231 (Benzene/ Cyclohexane)	2980, 2950, 2860 (CH) 1705, 1690 (CO) 1600 (CC)	2.8–3.6 (11H/m) 4.14 (1H/s) 6.06 (3H/s) 7.62 (3H/s)	60 MHz $CDCl_3$

When boiled in toluene, *(2)* loses nitrogen, passing into *(3)*, which rearranges into 6'-methoxy-*m*-terphenyl-4'-ol *(4)* on 12 hours' heating in xylene.

Methylation of *(4)* by dimethyl sulfate affords 4',6'-dimethoxy-*m*-terphenyl *(5)*[5], whose ^{1}H-NMR spectrum proves the positions of the substituents in *(5)* and *(4)*: the methoxy groups give a singlet (τ = 6.26), the proton in *o*-position thereto appears at τ = 3.48[6], and the *m*-proton appears at τ = 2.9. These two protons do not couple with each other, which indicates their *para* relation[6].

The pyrazoline derivative *(2)*, which also gives *(4)* on fairly long heating in xylene, isomerizes in a known manner[7] to 3a,6a-dihydro-4-methoxy-3a,6a-diphenylcyclopentapyrazol-6(1*H*)-one *(6)* when boiled in glacial acetic acid or methanol and also on chromatography on silica gel.

The pyrazolines *(2)* and *(6)* react with acetyl chloride to afford the 1-acetyl derivative *(7)*.

(2) and *(3)* are formed as soon as the components are brought together. Since the change of the yellow reaction solution to the violet color characteristic of cyclones is not

then is a CH_2 group inserted between the carbonyl groups. Enolization and methylation complete the reaction.

The exclusive formation of *(2)* accords with observations on the reaction of tetraphenylcyclone with diazomethane[8] and points to the differing stabilities of the two possible 1-pyrazolines.

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[1] Part of the projected Dissertation of *W. Kuhn*.

[2] A. H. S. thanks the Stiftung Stipendien-Fonds of the Verband der Chemischen Industrie for a Liebig Stipendium.

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An ESR Study of the Oxidation of Triethyl Phosphite by *tert*-Butoxy Radicals

By *Alwyn G. Davies, D. Griller*, and *B. P. Roberts*[*]

The radical reactions of phosphorus compounds are of considerable interest[1].

If di-*tert*-butyl peroxide Bu^tOOBu^t is photolyzed in the presence of a trialkylphosphane (R_3P with $R=CH_3$, C_2H_5, $(CH_3)_2CH$, $(CH_3)_2CH—CH_2$ or cyclo-C_6H_{11}), the *tert*-butoxyl radical brings about an S_H2 reaction at the phosphorus centre, and the displaced radical R· can be observed by ESR spectroscopy. When R = Me, the spectrum of the intermediate phosphoranyl radical *(1)*, $a_P = 618$ G is also apparent[2].

$$Bu^tO\cdot + PR_3 \rightarrow \underset{(1)}{Bu^tO\dot{P}R_3} \rightarrow Bu^tOPR_2 + R\cdot \qquad (1)$$

Under the same conditions, trialkyl phosphites [$(RO)_3P$ with $R=CH_3$, C_2H_5 or $(CH_3)_2CH$] were reported to show only the spectrum of the *tert*-butyl radical, and no intermediate phosphoranyl radical *(2)*[3] was detected[2].

$$Bu^tO\cdot + P(OR)_3 \rightleftharpoons \underset{(2)}{Bu^tO\dot{P}(OR)_3} \xrightarrow{k_2'} Bu^t\cdot + OP(OR)_3 \qquad (2)$$

We have studied the photolysis of di-*tert*-butyl peroxide in the presence of triethyl phosphite in cyclopentane, and have observed the ESR spectrum of both the phosphoranyl radical *(2)*, $R=C_2H_5$, and the *tert*-butyl radical; in dilute solutions, the spectrum of the cyclopentyl radical, which is formed in reaction (3), was also apparent.

$$Bu^tO\cdot + C_5H_{10} \xrightarrow{k_3} Bu^tOH + C_5H_9\cdot \qquad (3)$$

By monitoring the concentrations of these three radicals, Arrhenius parameters have been obtained for the overall reaction (2), and for the breakdown of the intermediate phosphoranyl radical.

The spectrum obtained by photolyzing a solution of di-*tert*-butyl peroxide (1.1 M) and triethyl phosphite (1.2 M) in cyclopentane at −85 °C in the cavity of an ESR spectrometer is shown in Figure 1[4]. The phosphorus-centered radical ($a_P = 891$ G, $g = 2.008$), to which we assign the structure *(2)*, $R=C_2H_5$, [**] shows no resolvable fine structure. Radical concentrations were measured against a ruby which was fixed in the ESR cavity[5].

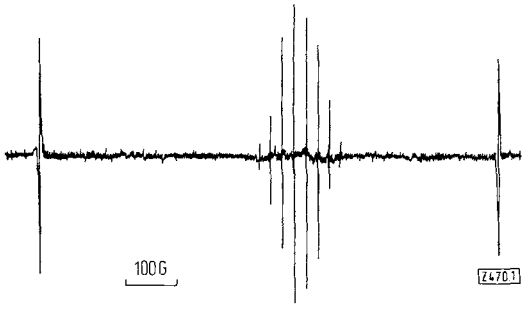


Fig. 1. ESR spectrum from irradiation of di-*tert*-butyl peroxide and triethyl phosphite in cyclopentane at −85 °C with UV light. Spectral parameters in the text have been corrected by the Breit-Rabi formula.

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[**] The radical $Bu^t\dot{P}(OC_2H_5)_3$ is excluded because photolysis of 2,2′-azoisobutane in the presence of triethyl phosphite gave only the spectrum of the *tert*-butyl radical.

The rate constant (k_2) for the overall reaction (2) was determined relative to k_3 by the method we have recently described[6, 7], by measuring the relative concentrations of the *tert*-butyl and cyclopentyl radicals formed from dilute solutions of triethyl phosphite (0.07 M) in cyclopentane containing di-*tert* butyl peroxide (1.1 M). An Arrhenius plot of the results gives

$$k_2/k_3 = (0.83 \pm 0.01)\exp(2960 \pm 180)/RT$$

At 130 °C $k_2/k_3 = 190$. This is to be compared with a value of about 600 which can be estimated from Walling and Pearson's analysis of the products from the thermal decomposition of di-*tert*-butyl peroxide in a mixture of triethyl phosphite and cyclohexane[8].

If the value of k_3 is taken to be[7]

$$k_3 = 1.0 \times 10^9 \exp(-5200/RT)\ \mathrm{l\,mol^{-1}\,s^{-1}}$$

we derive

$$k_2 = 6.7 \times 10^9 \exp(-2240/RT)\ \mathrm{l\,mol^{-1}\,s^{-1}}$$

and

$$k_2(30°) = 1.6 \times 10^8\ \mathrm{l\,mol^{-1}\,s^{-1}}$$

Thus although the reaction proceeds through an intermediate complex, it is one of the fastest bimolecular radical-molecule reactions which are known.

By the steady state approximation,

$$k_2' = [Bu^t\cdot]/[(2)]\{2k_t[Bu^t\cdot] + 2k_t'[(2)] + 2k_t''[Bu^tO\cdot]\}\ \mathrm{s^{-1}}$$

where the last three terms refer to the removal of *tert*-butyl radicals by their reactions with the radicals $Bu^t\cdot$, *(2)*, and $Bu^tO\cdot$ respectively. The last term can be neglected because the value of $[Bu^tO\cdot]$ is very small.

There is as yet no information on the rate of the reaction of phosphoranyl radicals *(2)* with alkyl radicals[9][***], and

[***] It should be possible to evaluate this term by experiments at different light intensities and by monitoring the decay of the ESR signals by the CAT technique [10].

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the second of these three terms might be similar in magnitude to the first[11]. If this second term is neglected, the reduced expression

$$k_2' = 2k_t[Bu^t]^2/[(2)]\ s^{-1}$$

gives an excellent Arrhenius plot which would correspond to

$$k_2' = (2.40 \pm 0.06) \times 10^{13} \exp(-9340 \pm 230)/RT\,s^{-1}$$

setting a lower limit to the value of k_2' at 30 °C of $4.4 \times 10^6\ s^{-1}$.

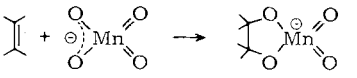
Received: June 26, 1971 [Z 470 IE]
German version: Angew. Chem. 83, 800 (1971)

[1,3]-Anionic Cycloaddition of 2-Azaallyllithium Compounds to Dienes[1][**]

By *Thomas Kauffmann* and *Rudolf Eidenschink*[*]

2-Azaallyllithium compounds undergo cycloaddition in preparatively useful yields to CC[2], CN[3], and NN double bonds[3] as well as to CC and CN triple bonds[4] with formation of five-membered heterocycles. Analogous reactions have been observed for a 2-azaallylsodium[5], 2-azaallylpotassium[5], and 1,2-diazaallyllithium compound[6]. We propose the term [1,3]-anionic cycloaddition for this type of reaction, of which the first stage of the Baeyer test leading to *(1)* can be regarded as the oldest example[7].

As expected, 1,3-dienes can also act as [1,3]-anionophiles[8]: By reaction (conditions: [9]) of equimolar amounts of the three 2-azaallyllithium compounds *(2)*[2], *(3)*[2], and

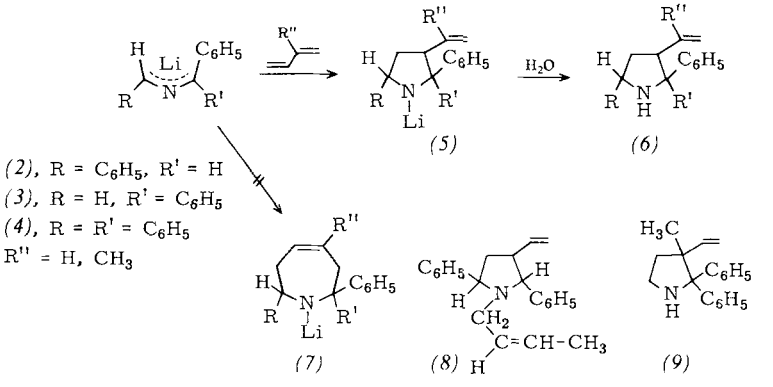


(1)

(4)[10] with butadiene or 2-methylbutadiene in THF/*n*-hexane (*ca.* 9:1) the pyrrolidines *(6)* listed in the Table were obtained *via* the cycloadducts *(5)*.

In the first experiment in the Table the yield of pyrrolidine of type *(6)* was decreased by further reaction of the cycloadduct to give the alkenylated product *(8)* (47%; *cis*- and *trans*-configuration of the *n*-butenyl group). In the fourth experiment the yield is decreased because cycloaddition of the 2-azaallyllithium compound to the electron-richer CC double bond of the 2-methylbutadiene leads to 3-methyl-2,2-diphenyl-3-vinylpyrrolidine *(9)* (13%) as well as to 3-(1-methylvinyl)-2,2-diphenylpyrrolidine [type *(6)*].

The structures of the new pyrrolidines obtained, which are oils whose yields are recorded in the Table, were proved by analyses and spectra (MS, NMR, IR), but the configuration of the substituents on the pyrrolidine ring is as yet uncertain. None of these products showed any sign of resolution into stereoisomers on gas chromatography, and the NMR spectra indicate sterically homogenous products. So the cycloadditions apparently occur stereospecifically. This and the non-appearance of seven-membered cycloadducts *(7)* signify a synchronous $[_\pi 4 + _\pi 4]$ process.

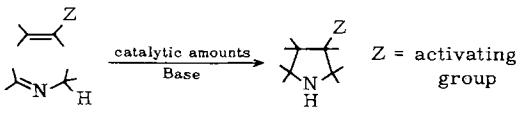


No.	2-Azaallyl-Li cpd.	Diene	Pyrrolidine deriv. *(6)*	Yield (%)	Salt	m.p. (°C)
1	*(2)*	1,3-Butadiene	2,5-Diphenyl-3-vinyl	36	Picrate	155
2	*(2)*	2-Methyl-1,3-butadiene	3-(1-Methylvinyl)-2,5-diphenyl	92	Picrolonate	234
3	*(3)*	1,3-Butadiene	2,2-Diphenyl-3-vinyl	91	Picrate	231
4	*(3)*	2-Methyl-1,3-butadiene	3-(1-Methylvinyl)-2,2-diphenyl	35	Picrate	171
5	*(4)*	1,3-Butadiene	2,2,5-Triphenyl-3-vinyl	35	Picrate	111

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The pyrrolidine *(6)* obtained in experiment 2 could be prepared, in 90% yield, also by treatment of one mol of the azomethine *N*-benzylidenebenzylamine in THF at 20°C with one mol of 2-methylbutadiene and a catalytic amount (0.05 mol) of lithium pyrrolidide. Apparently the lithium pyrrolidide formed in the addition process is able to metalate the azomethine smoothly. This base-catalyzed union of an azomethine *(10)* and an alkene, which is presumably not restricted to the special system discussed here, may lead to an industrially interesting process.



(10)

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[1] [1,3]-Anionic Cycloaddition, Part 4.—Parts 1—3 are assumed to be [2], [3], and [6].

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[4] *E. Köppelmann,* Dissertation, Universität Münster 1971; *K. Habersaat,* Diplomarbeit, Universität Münster 1971.

[5] *D. Berger,* unpublished work, Münster, 1971.

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[7] For other "precursors" see [3], note 3.

[8] *R. Eidenschink,* Diplomarbeit, Universität Münster 1971.

[9] The diene was always added at −65°C to a solution of the 2-azaallyllithium compound prepared at that temperature from the azomethine and lithium diisopropylamide, then warmed to 22°C. In experiment 5 only, the temperature was raised to 66°C.

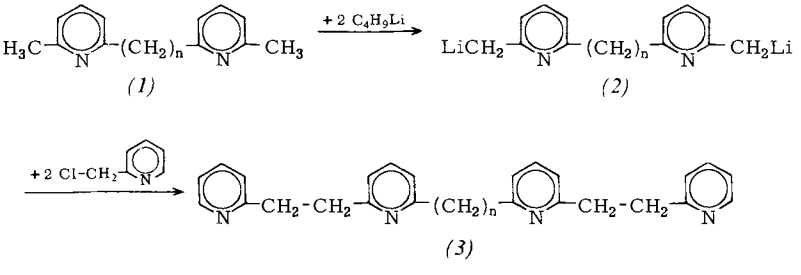
[10] Preparation from *N*-benzylidene(diphenylmethyl)amine by treatment with lithium diisopropylamide in THF at −65°C (at this temperature only *ca.* 20% metalation).

has been introduced for cyclically bridged arenes[3], we propose the name protophanes (πρῶτος = first) for the open-chain (unbranched or branched) compounds. This usage, which is in line with the occurrence of protophanes as precursors in the synthesis of cyclic phanes, should not be applied to simple molecules such as 1,4-diethylbenzene or 1,2-di-(2-pyridyl)ethane, but should be restricted to molecules containing at least three arene units (= single rings or fused arene systems) separated by aliphatic groups.

Syntheses of protophanes containing three or four pyridine rings linked by ethylene bridges[2] has been possible because *(1)*, $n=2$, is metalated selectively at the methyl groups by *n*-butyllithium in THF at −70°C. Corresponding metalation of *(1)*, $n=3$, 5, 6, 8, has now been carried out (CH_3/CH_2 metalation = 95—100/5—0; total metalation 91—98%) and has been used for synthesis of protophanes: the dilithium compounds *(2)* obtained from *(1)*, $n=3$, 5, 6, 8[8] and 2 mol of *n*-butyllithium react with 2-(chloromethyl)pyridine in THF to afford the tetranuclear compounds *(3)*.

The monolithium compounds *(4)* obtained from *(1)*, $n=3$, 5, 6, 8, and one mol of *n*-butyllithium afford the tetranuclear protophanes *(5)* on treatment with CuCl. Compounds *(5)* are obtained also, but in somewhat lower yield, on reaction of compounds *(4)* with 1,2-dibromoethane. In these cases the hexanuclear protophanes *(6)* could also be isolated from the reaction mixtures, being formed from two molecules of the monolithium compound *(4)* and one molecule of the dilithium compound *(2)* which are in equilibrium with the unmetalated compound *(1)* in THF.

The protophanes mentioned were separated from higher-molecular by-products and cyclic phanes by column chromatography (Brockmann Al_2O_3, activity II—III), and their structures were proved by elemental analyses, molecular-weight determinations, and spectroscopy (NMR, MS). The Table sets out the reaction conditions, the yields, and the astonishingly sharp melting points.



(1) *(2)* *(3)*

Pyridinoprotophanes with Alkylene Segments of Various Lengths[1][**]

By *Thomas Kauffmann, Gerhard Beissner,* and *Rüdiger Maibaum*[*]

Open chain bridged arenes such as *(3)*, *(5)*, and *(6)* and cyclically bridged arenes (= cyclophanes, phanes[3]) are related to one another in the same way as alkanes to cycloalkanes. It would therefore have been better to retain the name phanes for open-chain members and to name the cyclic ones all as cyclophanes. Since, however, "phane"

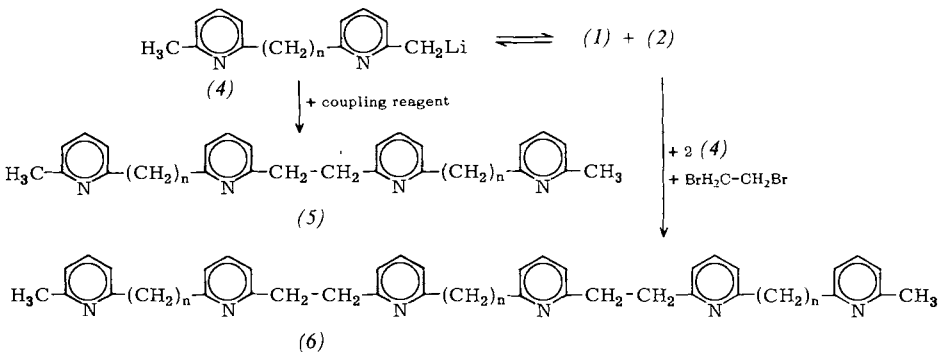
[*] Prof. Dr. Th. Kauffmann, Dipl.-Chem. G. Beissner, and R. Maibaum
Organisch-Chemisches Institut der Universität
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

The NMR spectra show in each case only three types of methylene proton, namely, for types *(3)* and *(5)/(6)*, respectively, in accord with representation *(7)*, H_A at $\tau=6.75$—6.90 or 6.78—6.90, H_B at $\tau=6.90$—7.39 or 6.90—7.46, H_C at $\tau=7.52$—8.84 or 7.56—9.18. Contrary to the case with protophanes of types *(5)* and *(6)* with $n=2$[9], here there is no resolution of the signals for methylene protons of the non-peripheral ethylene bridges.

IUPAC nomenclature is in practice inapplicable to complicated protophanes such as *(6)*. Such compounds can, however, be named easily and unambiguously if they are treated as alkanes in which individual carbon atoms have been replaced by arene rings or fused arene rings (*e.g.*, quinoline). The arene units could be denoted as phena (benzene), pyrida (pyridine), thiena (thiophene), *etc.* The ending "a" denotes a special nomenclature, so that there

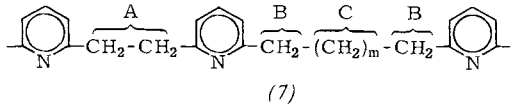
would be no need for a particular class term (*e.g.*, phane) at the end of the name. Side chains of the "parent hydrocarbon" (considered to be the longest C chain), when containing arene rings, could be named analogously. The nomenclature described here only in principle[10] has a ter would have been [15](1.4)benzenocyclophane and [12](1.5)naphthalenocyclophane). *Vögtle* and *Neumann* [7] defined phanes in general as cyclically bridged arenes and would like to have cyclopolyarenes included in that class although they do not have the characteristic juxtaposition of aromatic ("ph" in phan) and aliphatic units ("an" in phan) and thus possess totally different chemical properties.



Protophanes Type	n	Yield (%)	M. p. (°C)	Reaction conditions
(3)	3	35—38	88	1. *(1)* +2 mol of *n*-BuLi in THF [a] at −70°C (30 min)
	5	36—40	75—76	2. Add 1 mol of 2-(chloromethyl)pyridine and warm to 20°C
	6	37—39	76—77	3. Hydrolysis with H_2O
	8	41—44	78—80	
(5)	3	40—42	111—112	1. *(1)* +1 mol of *n*-BuLi in THF [a] at −70°C (30 min)
	5	36—39	79	2. Add 1 mol of CuCl, warm at 60°C (2 h)
	6	32—35	86	3. Hydrolysis with solution of KCN (60 g) in aqueous 25%
	8	38—40	84	KOH
(6) [b]	3	12—16	142—143	1. As for *(5)*
	5	18—20	110—111	2. Add 1 mol of 1,2-dibromoethane
	6	22—26	113	3. After 30 minutes' heating at 20°C, hydrolyze with water
	8	18—19	129—130	

[a] The THF always contained *ca.* 10% of *n*-hexane that was introduced with the *n*-butyllithium.
[b] The protophanes *(5)* were formed as by-products in 20—27% yields.

valued precursor in *Stelzner*'s a-nomenclature (*e.g.*, quinoline = 1-azanaphthalene) and would afford, *e.g.*, 1,12-di(2)-pyrida-4,9-di(2,6)pyrida-dodecane as the name for *(3)*, $n=4$.



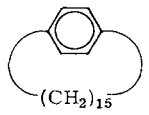
Particularly valuable is that a few further rules would enable cyclic phanes and polyarenes to be named analogously.

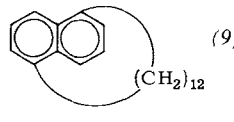
Received: July 5, 1971 [Z 473b IE]
German version: Angew. Chem. *83*, 795 (1971)

[1] Protophanes and Polyarenes, Part 2. — Part 1 is considered to be the communication given under Ref. [2].

[2] *Th. Kauffmann, G. Beissner, W. Sahm*, and *A. Woltermann*, Angew. Chem. *82*, 815 (1970); Angew. Chem. internat. Edit. *9*, 808 (1970).

[3] The term cyclophane was introduced [4] for compounds in which two benzene rings were bridged cyclically by a *para*-alkylene unit and was later [5] extended logically to any number of benzene rings linked cyclically by alkylene bridges. *Smith* [6] introduced "phane" (without the preceding "cyclo") as final syllable for cyclophanes that contained arene nuclei other than benzene; according to his system, for instance, *(8)* is [15]paracyclophane, but *(9)* is [12](1.5)naphthalenophane (bet-





[4] *D. J. Cram* and *H. Steinberg*, J. Amer. Chem. Soc. *73*, 5691 (1951).

[5] *W. M. Schubert, W. A. Sweeney*, and *H. K. Latourette*, J. Amer. Chem. Soc. *76*, 5462 (1954).

[6] *B. H. Smith*: Bridged Aromatic Compounds. Academic Press, New York 1964, p. 8.

[7] *F. Vögtle* and *P. Neumann*, Tetrahedron Lett. *1969*, 5329; Tetrahedron *1970*, 5847.

[8] Prepared by treatment of 2-(lithiomethyl)-6-methylpyridine with α,ω-dibromoalkanes in boiling ether (with $n=3, 5, 6, 8$, yields 31, 38, 36, 41%, m. p. 38—39, 28—30, 27—29, 33—34°C).

[9] *W. Jenny* and *H. Holzrichter*, Chimia *23*, 158 (1969).

[10] A detailed nomenclature proposal based on this system will shortly be published by us.

Organometallic Syntheses of Thiophene-Pyridine Combinations[1][**]

By *Thomas Kauffmann, Ekkehard Wienhöfer*, and *Annegret Woltermann*[*]

Arene rings can be contained in fused systems (type A ring systems), linked directly by single bonds (type B ring combinations, IUPAC ring assemblies[3], polyarenes[4]), or bridged by means of atoms not belonging to the arene rings (type C, cf. Ref. [2]).

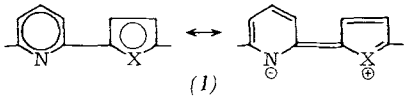
[*] Prof. Dr. Th. Kauffmann, E. Wienhöfer, and A. Woltermann
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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Ar—Ar—Ar Ar—(C)$_n$—Ar—(C)$_m$—Ar

B C

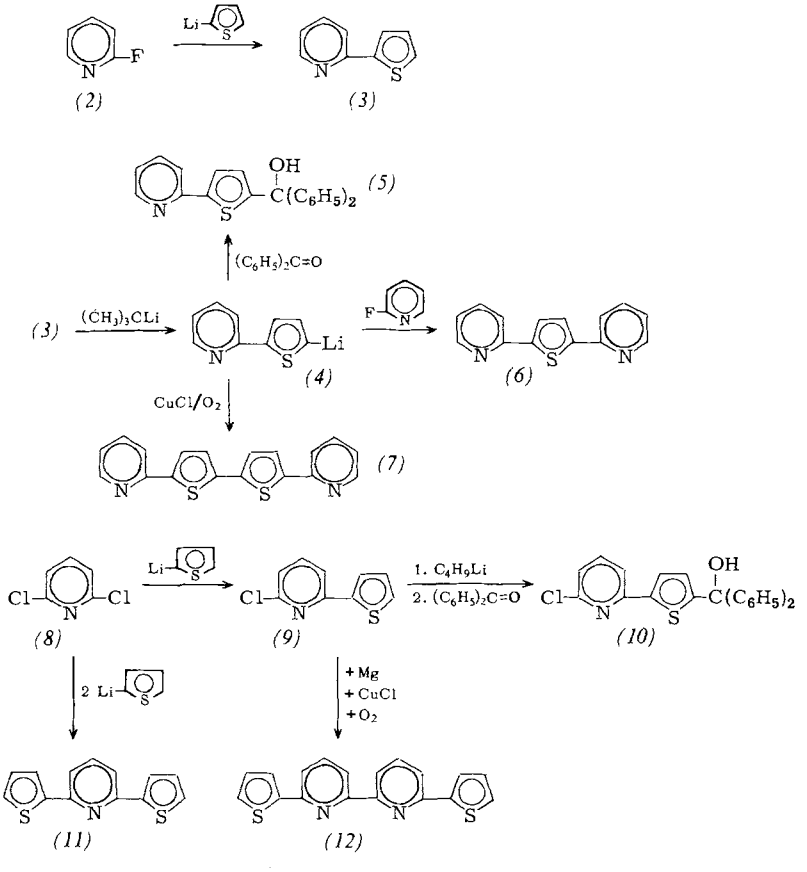
Whereas type A has been intensively studied, little is known about compounds of types B and C. This is surprising, particularly for type B; it should be extremely interesting to discover to what extent the arene systems of various structures (*i.e.* the cyclic atomic groups of organic chemistry distinguished by particularly low energy contents) can be connected in accordance with B to form longer unbranched or branched chains and into rings with various chain and ring members; and here it is noteworthy that polyarenes consisting homogeneously of benzene rings, pyridine rings (maximally 6[7]), or thiophene rings (maximally 7[8]) are thermally very stable.



(1)

We have first synthesized compounds of type B in which the possibility of mesomerism *(1)* should lead to a certain amount of exchange between π-electron-rich and π-electron-deficient nuclei and thus to alteration in the reactivities of the nuclei. (By π-electron rich we mean a system having an *excess* of π-electrons at the C atoms.)

Of the various ring combinations *(1)* in which X = O, S, or NCH_3, apparently only the thiophene derivative *(3)* (yield <4%[9]) is known. We were able to prepare this compound in 48% yield by treating 2-lithiothiophene *(2)* with one mol of 2-fluoropyridine. The chloro compound *(9)* was formed analogously from 2,6-dichloropyridine. These two biarenes were not attacked in the pyridine ring by *n*- or *tert*-butyllithium, but were metalated almost exclusively at the α-position of the thiophene ring[10]. Reaction of the lithium compound *(4)* obtained in this way with benzophenone gave the alcohol *(5)*, with 2-fluoropyridine gave the trisarene *(6)*, and with $CuCl/O_2$ gave the tetrakisarene *(7)*. Analogously the lithium compound



Reaction	Reaction conditions: Metalation	Reaction conditions: Reaction of metalated product	Product: Yield (%)	Product: M.p. (°C)
(2) → *(3)* [a]	*n*-BuLi (+thiophene); 0°C	2 h, +35°C	48	64 [d]
(3) → *(4)* → *(5)* [b]	*t*-BuLi; −60°C	2 h, +20°C	87	116—117 [d]
(3) → *(4)* → *(6)* [b]	*t*-BuLi; −60°C	in anisole [c], 5 h, +154°C	7	162—163 [e]
(3) → *(4)* → *(7)* [b]	*t*-BuLi; −60°C	3 h, +65°C	63	225—226 [e]
(8) → *(9)* [a]	*n*-BuLi (+thiophene); 0°C	3 h, +35°C	36	[f]
(8) → *(11)* [a]	*n*-BuLi (+thiophene); 0°C	5 h, +35°C	18	99 [d]
(9) → *(10)* [b]	*t*-BuLi; −60°C	2 h, +20°C	83	104—105 [d]
(9) → *(12)* [b]	Mg + CuCl; +60°C	with O_2 2.5 h, +60°C	5	206—208 [e]

[a] Solvent: ether (+ *ca.* 10% of *n*-hexane introduced with *n*-butyllithium).
[b] Solvent: THF (+ *ca.* 10% of *n*-hexane introduced with *n*-butyllithium).
[c] After THF has been distilled off.
[d] Colorless.
[e] Pale yellow.
[f] B.p. 112—114°C/0.1 torr.

obtained from *(9)* gave, on reaction with benzophenone, the alcohol *(10)*. Treatment of *(8)* with an excess of 2-lithiothiophene leads to the trisarene *(11)*, while the action of a magnesium/CuCl mixture followed by O_2 on *(9)* gave the tetrakisarene *(12)* that is isomeric with *(7)*.

The Table records the reaction conditions, yields, and properties of the compounds prepared; their structures appear to be proved by elemental analyses, mass and NMR spectra, and the methods of preparation. None of the compounds in the Table has been reported before with the exception of *(3)*.

From the mass spectra of the tetrakisarenes *(7)* and *(12)* it follows that the bond between one pyridine and one thiophene nucleus is approximately the same strength as that between two pyridine or between two thiophene rings. This is to be expected since, like polyarenes built homogeneously from thiophene or pyridine rings[7,8], long-chain "mixed" polyarenes are also thermally very stable.

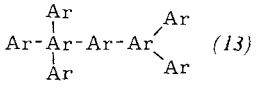
Received: July 5, 1971 [Z 473c IE]
German version: Angew. Chem. *83*, 796 (1971)

[1] *Protophanes and Polyarenes*, Part 3. — Part 2: [2].

[2] *Th. Kauffmann, G. Beissner*, and *R. Maibaum*, Angew. Chem. *83*, 795 (1971); Angew. Chem. internat. Edit. *10*, 740 (1971).

[3] To differentiate them from ring systems (condensed) and to draw attention to the enormous possibilities of combination (*e.g.*, 81 combinations of one pyridine and two imidazole rings), we describe as ring combinations those molecules in which a small number of aromatic or non-aromatic rings are joined by single bonds.

[4] The nomenclature of polyarenes is unsatisfactory; if individual names [5, 6] are generalized, open-chain polyarenes are denoted as polyaryls or polyarenes, but cyclic ones as polyarylenes. "Polyarenes" appears to us the better designation for the open-chain compounds with more than two arene rings, since only this is neutral with regard to the bonding state of the arene ring; this can be very variable, as shown by *(13)* with 1-, 2-, 3-, and 4-bonded arene nuclei. Macrocycles whose ring members consist only of arene nuclei should be called cyclopolyarenes.



(13)

[5] Cf. *e.g.* "Polythienyls", *H. D. Hartough*: Thiophene and Its Derivatives, p. 465 or "Polypyridines", *L. E. Tenenbaum*: Pyridine and Its Derivatives, Part Two, p. 224. Both in: The Chemistry of Heterocyclic Compounds. Interscience, New York 1952 and 1961; IUPAC Rules A-51 and A-52.

[6] Cf. *e.g.* "Hexa-*m*-phenylen": *F. Binning, H. Meyer*, and *H. A. Staab*, Liebigs Ann. Chem. *724*, 24 (1969); IUPAC Rule A-21

[7] *F. H. Burstall*, J. Chem. Soc. *1938*, 1662.

[8] *W. Steinkopf, R. Leitsmann*, and *K. H. Hofmann*, Liebigs Ann. Chem. *564*, 180 (1941).

[9] *H. Wynberg, T. J. van Bergen*, and *R. M. Kellog*, J. Org. Chem. *34*, 3175 (1969).

[10] Just as carboxylic acids and amides are more acidic than alcohols or amines, so *(3)* should be more acidic than thiophene.

The Arenology Principle[1][**]

By *Thomas Kauffmann*[*]

Dedicated to Professor Adrien Albert

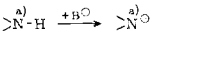
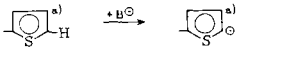
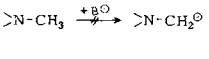
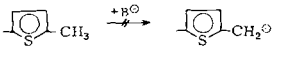
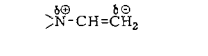
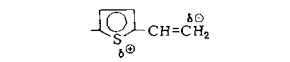
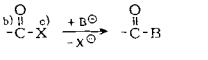
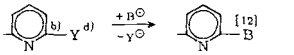
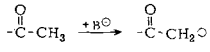
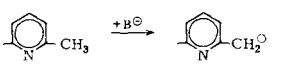
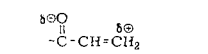
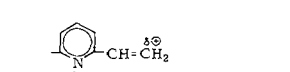
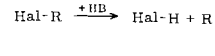
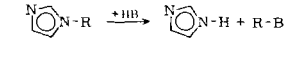
The extremely valuable division of arenes containing a hetero atom into π-electron-deficient and π-electron-rich arenes is due to *Albert*[3]. *Staab*[4] recognized that compounds with high acyl halide activity (azolides) are obtained by replacing the halogen of acyl halides by an azole group as in *(3)* of Table 2. We develop below a principle of wider application, whose value became apparent in studies of protophanes[5-7] and polyarenes[2,8].

The Arenology Principle: Organic chemistry deals, not only with the classical functional groups, but also with a second set of functional groups consisting of the heterocyclic arene (heteroaromatic) nuclei. The latter are arene-analogous (arenologous) to the classical functional groups since they can fullfil analogous functions: they undergo analogous reactions (sometimes only under activation by strong bases[9]) and make it possible for attached groups to undergo analogous reactions (Table 1).

π-Electron-rich arenes (furan, thiophene, 1-methylpyrrole, *etc.*[10]) are comparable with functional *groups that have* $+M$ *and* $-I$ *effect*, and mobile hydrogen (—OH, —SH, $—NH_2$, *etc.*); π-electron-deficient arenes (pyridine, pyrimidine, *s*-triazine, *etc.*) are comparable with functional *groups with* $—M$ *and* $—I$ *effect* (C=O, >C=N—, —C≡N, *etc.*). Azoles containing more than one N atom bound by way of an N atom correspond to halogen and other good negative leaving groups.

Whilst the parallel with regard to the polarization of attached groups has been recognized, insufficient attention has been paid to the fact that other properties of certain heterocyclic arenes indicate their possible use as functional ("arenofunctional") groups. If this were not so, it would be unintelligible why no attempt has been made to make specifically arenologous[11] models of elementary or particularly useful organic structures such as acid amides, acid halides, di- and poly-carbonyl compounds, di- and poly-amines, Nylon, Perlon, *etc.*, or to carry out fundamental reactions such as esterification or the Claisen condensation *systematically with arenofunctional groups* (our attempts in this direction: [2,5-8]).

Table 1. Characterization of the functions of functional groups by examples. a) nucleophilic activity; b) electrophilic activity; c) X = good negative leaving group; d) Y = H or good negative leaving group.

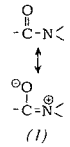
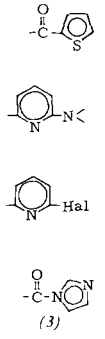
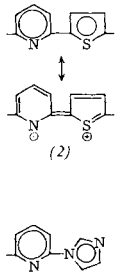
Functional group	Arenofunctional group
	
	
	
	
	
	
	

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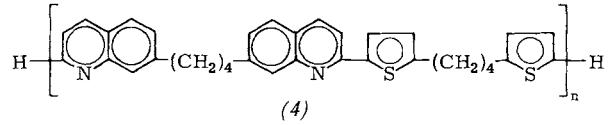
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

There are compound as well as simple functional groups, and from the former are derived semiarenologous and arenologous groups (Table 2). Although many semiarenologous groups are known and, in the case of the azolides [*(3)* of Table 2], are recognized as having functional activity, the arenologous type is as good as uninvestigated (cf. [2, 8]).

Table 2. Examples of compound functional groups and arenologs.

Normal	Semiarenologous	Arenologous
 *(1)*	 *(3)*	 *(2)*

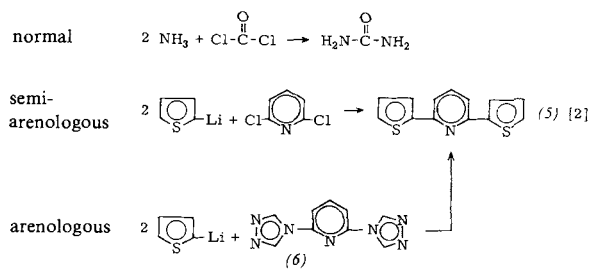
The bond energy between the arenofunctional groups in *(2)* (the CC bond) is probably higher (cf. Ref. [2]) than that between the functional groups of the acid amide group *(1)*, and this could be advantageous for arenologous Nylon [*e.g. (4)*] and Perlon types, whose synthesis is therefore being studied[7].



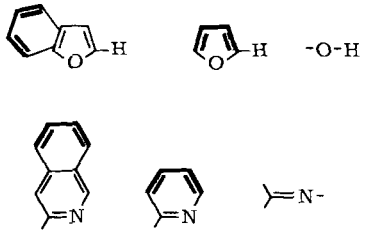
(4)

The chemical reactions that functional groups undergo can be divided into three types (Table 3). So far only the synthesis of "arenologous urea" *(5)* from 2,6-dichloropyridine has been carried out[2], but as yet not that starting from *(6)*.

Table 3. Urea syntheses as example of the application of the arenology principle to reactions.



The arenofunctional groups mentioned above are monocyclic 6π-electron systems. It is apparent that corresponding bicyclic 10π- (*e.g.* quinoline, cf. Ref. [8]) or tricyclic 14π-electron systems could fullfil analogous functions. The relationship between 6π-arenofunctional and normal functional groups is similar to that between 14π-, 10π-, and 6π-arenofunctional groups.

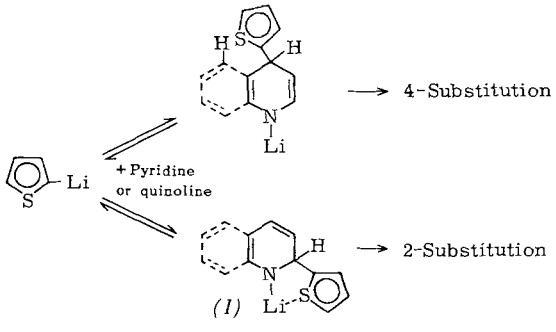


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Organometallic Syntheses of Thiophene-Quinoline Combinations[1][**]

By *Thomas Kauffmann, Jörg Jackisch, Hans-Joachim Streitberger*, and *Ekkehard Wienhöfer*[*]

Interaction of 2-thienylmagnesium iodide and pyridine in xylene at 130 °C gives 2- and 4-(2-thienyl)pyridine (together 4%[3]), but treatment with 2-thienylmagnesium bromide in ether at 35 °C (10%)[4] or with 2-lithiothiophene in THF at 60 °C (5%)[5] affords only the 4-isomer, for which chelate formation in the 2-adduct *(1)* is held responsible.



(1)

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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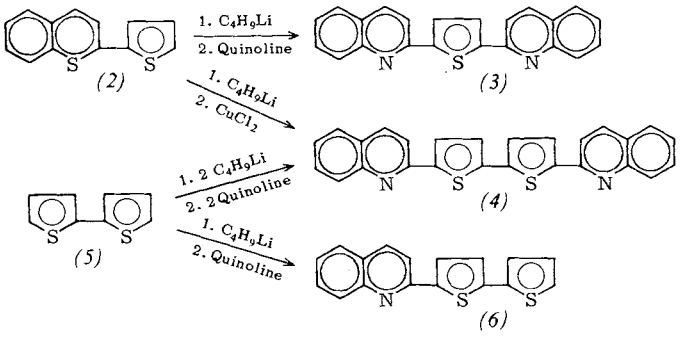
[9] Strong Lewis acids presumably can be used for activation in several cases.

[10] This order is not intended to state that the two types of functional groups correspond best when the heteroatoms correspond.

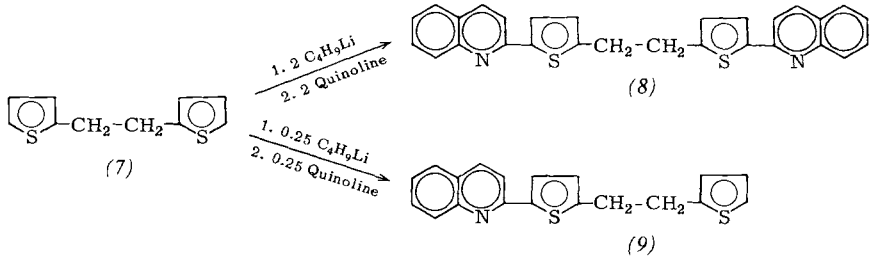
[11] In the sense of column 3 of Table 2, *i.e.* not semiarenologous.

[12] The pyridine nucleus reacts with nucleophiles analogously to a carbonyl group with good negative leaving groups. Only with bad negative leaving groups (aldehydes, ketones) does the carbonyl group behave differently (addition instead of substitution).

However, treating 2-lithiothiophene with quinoline at 20 °C by *Gilman*'s method[6] leads only to 2-(2-thienyl)quinoline *(2)* (38%), indicating steric hindrance of 4-addition by the *peri*-hydrogen atom of the quinoline. In the following reactions of the quinoline system with 2-lithiothiophene derivatives substitution is also only at the 2-position.



The yield of 2-(2-thienyl)quinoline *(2)* could be raised to 75% by causing the components to react at 45 °C [2 h in ether/*n*-hexane (2:1)], the 2-position of the thienyl group being provided by an analogous synthesis from 2-chloroquinoline instead of quinoline and by NMR spectroscopy. The lithium compound[6] obtained therefrom by *n*-butyllithium [yield 33% on the basis of the yield of alcohol (m. p. 221 °C) resulting from treatment with benzophenone] reacts with quinoline to give the trisarene *(3)* and with $CuCl_2$ to give the tetrakisarene *(4)*. As shown in the formula scheme and Table, compound *(4)* was accessible in higher yield by reaction of 2,2'-bithiophene and 2 mol of *n*-butyllithium with subsequent treatment with quinoline. The analogous reaction with one mol of the two reagents gave the trisarene *(6)* as main product.



Analogous methods afford compounds *(8)* and *(9)* which are homologs of *(4)* and *(6)* and of interest as starting materials for protophane syntheses[7]. Their preparation is possible because 1,2-di-(2-thienyl)ethane *(7)* (an "arenologous diamine", cf. Ref. [2]) is metalated by *n*-butyllithium in ether/*n*-hexane (9:1) only in the thiophene rings and not on the aliphatic bridge. The yield of *(8)* is considerably better than that of *(9)* since the monolithium derivative from *(7)* is in equilibrium with the dilithium compound and the unmetalated compound.

The Table records the reaction conditions, yields, and properties of the apparently new compounds prepared, their structures being proved by elemental analyses, mass and NMR spectra, and the method of their preparation.

Reaction	Treatment [a] of the metalated [b] product	Yield (%)	Product M. p. (°C)	Color
(2) → *(3)*	2 h, 35 °C	14	189—190	Yellow
(2) → *(4)*	3 h, 35 °C	14	250—251	Yellowish-red
(5) → *(4)*	1 h, 35 °C	37		
(5) → *(6)*	1 h, 35 °C	40 [c]	142	Yellow
(7) → *(8)*	2 h, 35 °C	57	189	Pale yellow
(7) → *(9)*	2 h, 35 °C	24 [d]	87	Pale yellow

[a] Solvent: diethyl ether (+ *ca.* 10% of *n*-hexane introduced with *n*-butyllithium); in the reaction *(2)* → *(4)* an additional 10% of THF.
[b] Metalation always with *n*-butyllithium at 0 °C (30 min).
[c] 26% of *(4)* formed as by-product.
[d] Yield calculated on *n*-butyllithium which was used in excess to suppress the formation of *(8)*.

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Direct Transformation of the Second Excited Singlet State of Benzene into Dewar-Benzene

By *D. Bryce-Smith, A. Gilbert*, and *D. A. Robinson*[*]

We have found that the S_2 state of benzene (but not the S_1 state) can isomerize directly into Dewar-benzene (bicyclo-[2.2.0]hexa-2,5-diene) by a symmetry allowed process which appears to provide the first example of a non-dissociative photochemical reaction from an upper excited singlet state.

Irradiation of liquid benzene under nitrogen at 254 nm populates the S_1 state (^1B_2u) and thence the T_1 state (^3B_1u), and gives the benzene isomers fulvene[1] and benzvalene[2], but no trace of Dewar-benzene. On the other hand, this latter isomer is among those formed by irradiation of liquid benzene over the 160—210 nm range, a process which directly populates both the S_2 (^1B_1u) and S_3 (^1E_1u) states of benzene[3]. The interesting question arises whether Dewar-benzene is being formed by a hitherto unknown type of *direct* isomerization of the S_2 and/or S_3 states: such transformations would be symmetry allowed, as would that of the T_1 state, but would not be thus allowed from the S_1 or S_0 states[4]. It was therefore desirable to identify more precisely the state of benzene which transforms into Dewar-benzene.

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Use of a microwave-generated discharge in argon/iodine[5] as radiation source (λ 206 nm) has made possible the irradiation of liquid benzene specifically in the $S_0 \rightarrow S_2$ band (λ_{max} 203 nm) without direct population of the S_1 state. Such irradiation of liquid benzene under standardized conditions (20 °C, 90 min, 2-ml samples) led typically to concentrations of Dewar-benzene, fulvene, and benzvalene of 30 ± 3, 50 ± 5, and 150 ± 10 ppm, respectively (GLC retention times, UV-spectrum of fulvene, half-lives of Dewar-benzene and benzvalene). The amounts and proportions of these isomers were the same from both air-saturated and argon-saturated benzene[**]. Thus the S_2 state of benzene is clearly implicated at some stage in the formation of Dewar-benzene, but these results on their own do not exclude the intermediacy of S_0, S_1, or triplet states produced from the S_2 state by internal conversion. The intermediacy of the S_0 and S_1 states in the formation of Dewar-benzene is rendered improbable by the absence of this isomer from the products of prolonged irradiations (*e.g.* 48 h) of liquid benzene in the $S_0 \rightarrow S_1$ band, both at 254 nm and over the whole band. One could only reconcile the intermediacy of S_0 or S_1 states with this evidence by the rather strained postulation of the need for some critically high vibrational levels inaccessible by direct irradiation in the $S_0 \rightarrow S_1$ band, and, as noted above, the transformations would be symmetry forbidden. The idea of vibrationally excited intermediates also seems at variance with the observed need for a liquid- rather than a gas-phase[3].

The possible intermediacy of triplet states of benzene in the formation of Dewar-benzene was tested by comparison of the rate of formation of Dewar-benzene from pure benzene with that from dilute solutions of benzene in *cis*-cyclooctene and cyclooctane. *cis*-Cyclooctene acts as an energy acceptor from T_1 benzene, giving the *trans*-isomer[6], and other olefins are well known to behave similarly[7]. In fact, irradiation of 10% solutions of benzene in *cis*-cyclooctene at 206 nm as above surprisingly increased the rates of formation of Dewar-benzene, fulvene, and benzvalene approximately 20-fold in comparison with the rates from pure liquid benzene under comparable conditions, and a similar degree of insensitivity to dissolved air was observed[***]. A similar increase (22-fold) was found with the use of cyclooctane as medium, so the dilution effect is physical rather than chemical in nature. The greatly increased rate of formation of Dewar-benzene in the presence of the olefin rules out any appreciable contribution from triplet benzene as an intermediate. Thus the evidence leaves S_2 benzene as the only reasonable direct precursor of Dewar-benzene.

The question whether Dewar-benzene can also arise from S_3 (^1E_1u) benzene was investigated by the use of an oxygen lamp emitting over the range *ca.* 160—220 nm[3], and a filter of 0.98-M aqueous LiCl to isolate the $S_0 \rightarrow S_2$ band when necessary. It was found that Dewar-benzene can also arise from population of the S_3 state: the results are consistent with direct isomerization of this state or of some state (*e.g.* S_2 benzene) derived from it.

It is interesting that *Braun, Kato,* and *Lipsky* found that **the internal conversion** efficiency from upper electronic states to the S_1 state (which is normally unity for most organic molecules that have been studied in dilute solution) is significantly less than unity in the cases of benzene and some methylbenzenes[9]. The present results suggest that part at least of the discrepancy can be attributed to a tendency for 1,4-bonding in the S_2 state of benzene.

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[**] The effect of the atmosphere on the process was examined for samples irradiated for 10 min since with the argon-saturated solutions significant amounts of an opaque polymer formed on the cell windows when the irradiation time was greater than *ca.* 30 min.

[***] The same mixture of cyclooctene-benzene 1,3-adducts was formed as is produced by irradiation at 254 nm, a result which suggests that higher excited states of benzene were not directly involved in the intermolecular cycloaddition process: cf. ref. [8].

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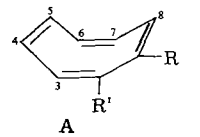
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Inhibition of Bond Exchange in Cyclooctatetraenes

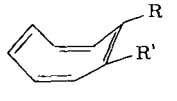
By *D. Bryce-Smith, A. Gilbert*, and *J. Grzonka*[*]

The [4*n*]annulenes so far studied exhibit (a) bond-alternation, and (b) bond-exchange[1-3]. Previous workers have shown that the rate of bond-exchange in the cyclooctatetraene ring tends to be decreased by mono- and 1,2-disubstitution, and that in the latter case the equilibrium favors the less overcrowded tautomer A[2-5]. We now report NMR and chemical evidence which, taken together, suggests that certain 1,2-disubstituted cyclooctatetraenes exist exclusively in form A.

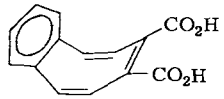
Dimethyl cyclooctatetraene-1,2-dicarboxylate *(1)* shows an NMR spectrum (Table) which remains unchanged over the temperature range −40 to +200 °C, apart from minor



A

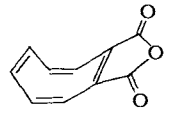


B

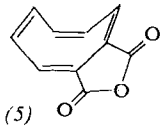


(3)

(1), R = R' = CO_2CH_3
(2), R = R' = CO_2H
(6), R = C_6H_5, R' = CO_2CH_3



(4)



(5)

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band shifts. The apparent lack of coupling between H_4H_5 and H_6H_7 is surprising, but another example of this is known[7]. The tabulated data are inconsistent with the presence of form B: cf. refs.[3, 7]. It is estimated that any contribution from form B greater than 2% would have been detected. Analysis of the NMR spectrum of the corresponding 1,2-dicarboxylic acid *(2)* leads to a similar conclusion (see Table).

Table. NMR spectra of compounds *(1)*, *(2)*, and *(6)* (interpreted as in refs. [2, 3, 6, 7]). The spectra are independent of temperature.

Compound, solvent	Signals (τ)	Assignment
(1)	2.94 (2H/d), $J = 3.0$ Hz	H-3, H-8, form A
CCl_4	4.02 (2H/d), $J = 3.0$ Hz	H-4, H-7, form A
	4.09 (2H) [a]	H-5, H-6, form A
	6.33 (6H/s)	methyl ester protons
(2)	2.88 (2H/d)	H-3, H-8, form A
$(CD_3)_2CO$	3.96 (4H/asym. m)	H-4—H-7, form A
	3.5 (2H/br. s)	carboxylic acid protons
(6)	2.85 (s) }	aromatic protons
CCl_4	2.79 (s) [b] } 6H	+H-3, form A
	3.75—4.40 (5H/m)	H-4—H-8
	6.58 (3H/s)	methyl ester protons

[a] Irregular singlet.
[b] Shoulder.

That none of form B is in fact present is also suggested by the reported inability of the dicarboxylic acid *(2)* to form a cyclic anhydride under normal conditions[8]. In contrast, benzocyclooctatetraene-7,8-dicarboxylic acid, which must exist solely in form *(3)*, readily forms a stable cyclic anhydride[6].

We now report that the acid *(2)* can be induced to form a cyclic anhydride in low yields when treated with ethereal dicyclohexylcarbodiimide. In contrast with the anhydride from acid *(3)*, this new anhydride is highly unstable and polymerizes rapidly. Yet fresh samples, obtained with difficulty, showed a parent peak in the mass spectrum and had IR and NMR spectra consistent with the presence of vinyl protons only (τ 3.7—4.45 in $C_6D_6/(CD_3)_2CO$). Since the properties appear to exclude the obvious structure *(4)*, we are obliged to consider the apparently more strained structure *(5)* as the only one consistent with the experimental observations. The apparent failure to stabilize by isomerization to form *(4)* is remarkable. The strong, apparently exclusive, preference for form A in the present examples may result more from steric than from electronic factors since the NMR spectrum (Table) of *(6)*[9] shows that it also occurs only in form A.

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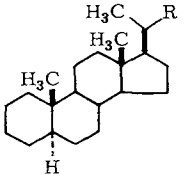
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First Identification of a Steroid Carboxylic Acid *in* Petroleum[1]

By *Wolfgang K. Seifert, Emilio J. Gallegos,* and *Richard M. Teeter*[*]

In a recent publication[2], we reported forty new classes of carboxylic acids in a Californian petroleum of Pliocene age (10 million years old). We now wish to report the identification of 23,24-bisnor-5a-cholanic acid *(1a)* in the same oil.



(1a), R = COOH
(1b), R = CH_3
(1c), R = CH_2D
(1d), R = CH_2OH
(1e), R = CH_2-O-SO_2-$C_6H_4CH_3$
(1f), R = $COOCH_2(CF_2)_6H$
(1g), R = CH_2CH_2COOH

A narrow fraction of carboxylic acids (fraction D-4[3], representing 1.6% of all acids and 0.04% of the petroleum) was converted by parallel reductions to hydrocarbons and deuterium-labeled hydrocarbons (in the position of the original carboxylic acid group) *via* the alcohols and *p*-toluenesulfonates using $LiAlH_4$ and $LiAlD_4$ in the last step[4]. The hydrocarbon and deuteriohydrocarbon samples were then further fractionated in parallel by silica gel and gel permeation chromatography (GPC) using previously described techniques[4]. Gas chromatography (GC) of a selected GPC fraction (100-foot by 0.02-inch ID capillary column, coated with OV 17) in combination with mass spectrometry (AEI MS-9) led to the identification of compounds *(1b)* and *(1c)*, respectively, thus showing the acid to have structure *(1a)*.

Proof of structure was obtained by: 1. Synthesis of 23,24-bisnor-5α-cholane *(1b)* by Wolff-Kishner reduction of 3-oxopregn-4-ene-20β-carbaldehyde and subsequent catalytic hydrogenation with PtO_2 in acetic acid. The resulting mixture of *(1b)* and the stereoisomeric 5β-hydrocarbon was separable by preparative GC (6 m by 6 mm OD column, 3% OV 17 on Gas-Chrom Q) and the products distinguishable by mass spectrometry; 2. Synthesis of *(1c)* by chromic acid oxidation of 3β-hydroxy-23,24-bisnor-5α-cholanic acid to the corresponding ketone and subsequent Wolff-Kishner reduction to give acid *(1a)*; the latter was converted[4] to deuterium-labeled hydrocarbon *(1c)* *via* alcohol *(1d)* and *p*-toluenesulfonate *(1e)* with $LiAlD_4$. Mass spectral fragmentation patterns and gas chromatographic retention times of synthetic labeled *(1c)* and unlabeled *(1b)* hydrocarbons were identical with those obtained from the naturally occurring acid; 3. The mass spectrum of synthetic ester *(1f)* was identical with that obtain-

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ed on GC-MS of the original acid fluoroheptyl ester mixture[5] at the retention time of ester *(1f)*.

In addition, two stereoisomeric C_{24}-steroid carboxylic acids were identified. Although structural proof is not complete, present results suggest that they are 5α- *(1g)* and 5β-cholanic acids.

The significance of this work is that these are the first polycyclic naphthenic carboxylic acids ever reported in petroleum as individual compounds; and on top of this they possess biological precursor hydrocarbon skeletons and, therefore, are geochemically significant. Animal bile acids are considered to be the most likely precursors.

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[1] Part of this work was presented at the Gordon Research Conference of Organic Geochemistry, Holderness, New Hampshire, September 1970, and at the Pacific Conference of Chemistry and Spectroscopy, San Francisco, California, October 1970.

[2] *W. K. Seifert* and *R. M. Teeter*, Anal. Chem. *42*, 180, 750 (1970).

[3] *W. K. Seifert* and *W. G. Howells*, Anal. Chem. *41*, 560 (1969).

[4] *W. K. Seifert, R. M. Teeter, W. G. Howells*, and *M. J. R. Cantow*, Anal. Chem. *41*, 1638 (1969).

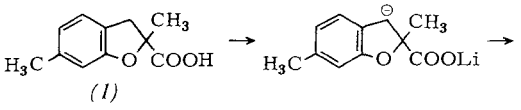
[5] *W. K. Seifert* and *R. M. Teeter*, Anal. Chem. *41*, 786 (1969).

Ring Expansion in the Benzofuran Series

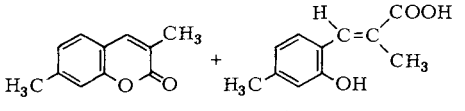
By *Bernard Libis* and *Ernst Habicht*[*]

2,3-Dihydro-6-methylbenzofuran-2-carboxylic acid[1] is converted into 2,3-dihydro-2,6-dimethylbenzofuran-2-carboxylic acid *(1)* (for procedure see Ref. [2]).

If compound *(1)* is treated with 2.2 mol. equiv. of lithium diisopropylamide at 0°C under N_2, the reaction mixture turns orange and a benzyl anion is formed. The dihydrofuran ring is cleaved between atoms 1 and 2, and acidification gives the known[3] coumarin *(2)* as the major product. The acid *(3)*, m. p. 200°C, whose stereochemistry precludes ring closure, appears as a minor product.

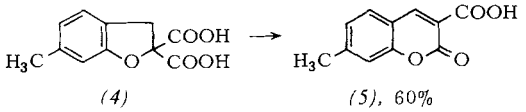


(1)



(2), 70% *(3)*, 10%

2,3-Dihydro-6-methylbenzofuran-2-carboxylic acid gives the dicarboxylic acid *(4)* when treated according to Ref. [2] and on adding CO_2. Reaction of *(4)* with 3.3 mol. equiv. of lithium diisopropylamide furnishes the known[4] coumarincarboxylic acid *(5)*.



(4) *(5)*, 60%

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We consider it remarkable that an anion should be formed β to the COOLi group, which leads to destabilization of the ether linkage and thereby to a reversal of the Perkin coumarin-benzofuran ring contraction. The reaction probably represents a route to hitherto inaccessible coumarins and *o*-coumaric acid derivatives.

Elemental analyses, IR and NMR spectra were all compatible with the above formulations.

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[1] *B. Libis* and *E. Habicht*, Belg. Pat. 733768 (1969), Geigy SA.

[2] *P. E. Pfeffer* and *L. S. Silbert*, J. Org. Chem. *35*, 262 (1970); *P. L. Creger*, J. Amer. Chem. Soc. *89*, 2500 (1967).

[3] *T. Nakabayashi* and *K. Yamasaki*, J. Pharm. Soc. Japan *74*, 590 (1954).

[4] *P. Chuit* and *F. Bolsing*, Bull. Soc. Chim. France *35*, 82.

Diethylborylation and Determination of Water with Activated Triethylborane

By *Roland Köster, Klaus-Ludger Amen, Hans Bellut*, and *Wolfgang Fenzl*[*]

Protolyses of trialkylboranes to yield alkane and *O*- or *N*-alkylboryl derivatives according to

$$R_3B + H{-}X \longrightarrow R_2B{-}X + RH$$

R = C_2H_5, C_3H_7, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$
X = O-alkyl, O-aryl, O-acyl, O—SO_2-alkyl, —O—SO_2-aryl, O—N=C-$alkyl_2$, O—N=C-$aryl_2$, N-$alkyl_2$, N-$allyl_2$, NH-aryl

proceed at differing rates, depending upon R and X. In general, trialkylboranes react with carboxylic acids[1] at about room temperature. In contrast, temperatures of 160—170°C are necessary for reaction of alcohols[2] or phenols[2], 170—200°C for dialkylamines[2], and about 100°C for alkane- and benzenesulfonic acids[3]. At these temperatures certain functional groups can be reduced by transiently formed B—H bonds (dehydroboronation) during the reaction.

We have found that protolyses of triorganoboranes can be considerably accelerated by catalytic amounts of pivalic acid or various pivalic acid derivatives:

$$(CH_3)_3C{-}COX,\ X = e.g.\ (C_2H_5)_2B{-}O > (CH_3)_3C{-}CO{-}O{-}CH_2{-}CH_2O \gg (CH_3)_3C{-}CH_2O > C_2H_5O$$

Triethylborane to which 0.1 to 1 mol-% of pivalic acid has been added reacts rapidly and quantitatively with water or alcohols at room temperature, one of its ethyl groups being eliminated as ethane.

$$2(C_2H_5)_3B + H_2O \xrightarrow{Cat.} (C_2H_5)_2BOB(C_2H_5)_2 + 2C_2H_6$$
$$Cat. = (C_2H_5)_2B{-}O{-}CO{-}C(CH_3)_3$$

This reaction can be utilized for a very simple determination of the water content of numerous hydrates of metal salts (see Table) with the aid of triethylborane/diethylboryl pivalate (b. p. 54°C/8 torr). The salts nearly always remain

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undissolved and can readily be isolated in the anhydrous state.

Like triethylborane, trimethyl-, tripropyl-, triisopropyl-, and triisobutylborane also react considerably faster with water, alcohols, or phenols on addition of pivalic acid.

Table. Determination [a] of water content of hydrates with triethylborane in the presence of diethylboryl pivalate.

Hydrate [b]	H_2O (%) [c]			$\frac{found}{calc.} \times 10^2$	
	calc. [b]	found [d] (with catalyst)	found [e] (without catalyst)	with catalyst [d]	without catalyst [e]
$Li_2SO_4 \cdot H_2O$	14.08	13.66	11.85	97.2	84.2
$Na_2S \cdot 9\,H_2O$	67.51	64.94	11.60	96.4	17.2
$Na_2S_2O_3 \cdot 3\,H_2O$	36.29	36.70	33.58	101.1	92.6
$Na_3PO_4 \cdot 12\,H_2O$	56.87	57.64	7.54	101.1	13.2
$Na_2Cr_2O_7 \cdot 2\,H_2O$	12.09	12.18	12.29	100.8	101.7
$NaVO_3 \cdot 4\,H_2O$	37.15	38.98	24.34	104.8	65.6
$MgSiF_6 \cdot 6\,H_2O$	39.38	39.51	16.48	100.1	41.8
$CaCl_2 \cdot 4\,H_2O$	39.37	39.70	28.91	100.9	73.5
$Ca(NO_3)_2 \cdot 4\,H_2O$	30.51	31.43	27.61	102.9	90.4
$Ca(SCN)_2 \cdot 4\,H_2O$	31.56	31.79	29.96	100.5	95.5
$MnCl_2 \cdot 4\,H_2O$	36.41	37.40	32.46	102.4	90
$FeCl_2 \cdot 4\,H_2O$	36.25	36.17	34.10	100	94.6

[a] Volumetric determination of the ethane liberated.
[b] Commercial samples, water contents according to manufacturers' specifications.
[c] The determinations can be carried out much more rapidly and at lower temperatures (20—50 °C) in the presence of catalyst, cf. [d] and [e].
[d] Evolution of ethane is exothermic and is generally complete after 5 min. The reaction mixture is then heated to boiling. The values obtained are reproducible. The considerable deviations from the calculated H_2O contents are due to the impurity of the commercial hydrates.
[e] Values obtained after 1 to 2 hours' heating in boiling triethylborane.

However, the catalyzed protolyses of the trialkylboranes BR_3 proceed at varying rates, in the order:

$$R = C_2H_5 > C_3H_7 \gg CH(CH_3)_2 \gg CH_2CH(CH_3)_2$$

Whereas even at temperatures above 100 °C only one alkyl group of the trialkylboranes reacts with alcohols, triphenylborane in the presence of diethylboryl pivalate is already degraded to boric acid at about 100 °C.

We have used catalyzed protolysis to prepare a large number of alkoxy- and aryloxydialkylboranes, some of which have functional groups such as C=C or C≡C bonds or NO_2 groups in the organic residue RO. The dialkylboryl derivatives of alkane- and benzenesulfonic acids were also obtained in high yields.

Sulfuric acid, phosphoric acid, boric acid, and iodic acid are also esterified with the diethylboryl group in the presence of diethylboryl pivalate at room temperature. In the absence of catalyst the higher temperatures required for the reaction usually result in mixtures of boron-containing and the boron-free acid anhydrides being formed.

Diethylborylation of polyhydroxy compounds also proceeds particularly smoothly on addition of pivalic acid. The hydroxyl group content of soluble, and also of insoluble, compounds, *e.g.* starch and cellulose, can therefore be accurately determined. Introduction of *O*-diethylboryl protective groups into sugars and sugar derivatives is also of preparative interest. The per-diethylborylated monosaccharides and their derivatives, *e.g.* 1,2,3,4,5-pentakis(diethylboryl)-D-(+)-glucose (b. p. 136 °C/0.001 torr), 2,3,4,6-tetrakis(diethylboryl)-α-methyl-D-(+)-glucoside (b. p. 130 °C/0.001 torr), 2,3,5,6-tetrakis(diethylboryl)-L-(+)-ascorbic acid, which are readily soluble in hydrocarbons, can be vacuum distilled without decomposition. The diethylboryl groups can be removed quantitatively and under extremely mild conditions by treatment with methanol. The boron-free sugar is obtained after the azeotropic mixture of methoxydiethylborane (b. p. 88.8 °C/770 torr; $n_D^{20} = 1.3869$) and methanol [$CH_3OB(C_2H_5)_2$: CH_3OH = *ca.* 1:2.8; b. p. 59.7 °C/770 torr; $n_D^{20} = 1.3620$; $d_4^{20} = 0.7675$] has been distilled off.

Introduction of the diethylboryl group into numerous NH compounds is also facilitated by the presence of pivalic acid derivatives. In addition to pyrrole and its derivatives[4], ammonia, amines, hydrazines, and carboxamides and carbohydrazides all react under milder conditions than in the absence of catalyst. Aldo and keto phenylhydrazones as well as phenylosazones also react under relatively mild conditions with "activated" triethylborane. In general, NH compounds react at 50—80 °C in the presence of diethylboryl pivalate. Temperatures of about 140 °C are required for ammonia and some mono- and dialkylamines.

Bis(diethylboryl)sulfate:

Sulfuric acid (98%; 15.6 g, *i.e.* 345 mg-atom of $H^{\oplus}$) is added dropwise over about 2 h to triethylborane (79 g, 806 mmol) containing diethylboryl pivalate (*ca.* 0.5 ml). The temperature rises to about 50 °C. Ethane (7.32 l, 327 mmol) is evolved. A clear pink liquid results from which a small amount of dark solid precipitates. Vacuum distillation yields firstly 51 g of a mixture (triethylborane and tetraethyl diboroxide), b. p. up to 25 °C/15 torr, and then 30 g (81%)[5] of bis(diethylboryl) sulfate, b. p. 66—67 °C/0.001 torr; 1.9 g of residue was left in the distillation flask.

Borylation of Cellulose:

Triethylborane (6.3 g, 64.3 mmol) containing 0.1 ml diethylboryl pivalate is added dropwise to a stirred suspension of cellulose (2.7 g, 16.65 m equiv) in 40 ml heptane at 60—70 °C (bath) over a period of 70 min. 700 Nml of ethane are evolved during the addition. Following a further

1.5 hours at 70—80 °C a total of 1135 Nml (101%) ethane is evolved. The voluminous white solid is filtered off and washed three times with pentane before being vacuum dried (yield 5.85 g, 96%). Found 5.84% B (on C)[6], calc. 5.90% B (on C). The per-*O*-diethylborylated cellulose is insoluble in both aliphatic and aromatic hydrocarbons as well as in carbon tetrachloride.

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German version: Angew. Chem. *83*, 805 (1971)

[1] Cf. *D. B. Bigley* and *D. W. Payling*, J. Inorg. Nucl. Chem. *33*, 1157 (1971), and further literature cited therein.

[2] *B. M. Michailow*, *W. A. Wawjer*, and *Ju. N. Bubnow*, Doklady Akad. Nauk SSSR *126*, 575 (1960); Chem. Abstr. *54*, 261 (1960).

[3] *S. Trofimenko*, J. Amer. Chem. Soc. *91*, 2139 (1969).

[4] *H. Bellut* and *R. Köster*, Liebigs Ann. Chem. *738*, 86 (1970).

[5] Based on reacted amount of sulfuric acid (165 mmol).

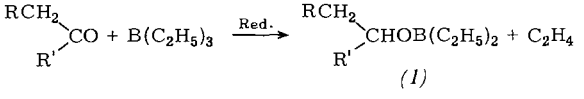
[6] Determined using trimethylamine *N*-oxide, see *R. Köster* and *Y. Morita*, Liebigs Ann. Chem. *704*, 70 (1967).

Reactions of Dialkyl Ketones with Triethylborane

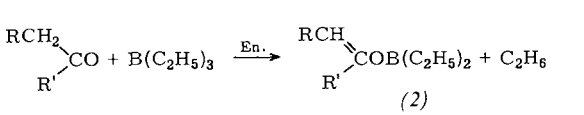
By *Wolfgang Fenzl* and *Roland Köster*[*]

Enolizable aldehydes and ketones do not generally react with trialkylboranes below 100 °C. Above this temperature reduction (Red.) and enolysis (En.) compete with each other, depending upon the carbonyl compound and trialkylborane used. For example, diethyl ketone and triethylborane react at 150 °C to give an almost equimolar mixture of ethylene and ethane. The boron-containing products are 3-diethylboryloxypentane *(1a)* and 3-diethylboryloxy-2-pentene *(2a)* (see Table).

We have found that, like the protolysis of trialkylboranes with hydroxy compounds[1], the enolysis of trialkylboranes with certain carbonyl compounds can be greatly accelerated by pivalic acid derivatives $(CH_3)_3CCOOR$, *e.g.* with $R=BR'_2$ or $CH_2CH_2—O—CO—C(CH_3)_3$. Depending



(1)



(2)

upon the alkyl groups of the dialkyl ketones, the reaction furnishes substituted vinyloxydiethylboranes *(2)* (yield 60—98%), which are important for additions to nitriles[2].

Table. Yields of diethylboryl enolates *(2)* and ethane in the reaction of ketones with triethylborane in the presence of diethylboryl pivalate.

	R	R'	Conversion (%)	Yields *(2)* (%) [a]	ethane (%)
(a)	CH_3	C_2H_5	100	82	98
(b)	C_2H_5	C_3H_7	100	82	98
(c)	CH_3	C_6H_5	25	60	93

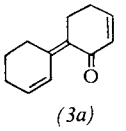
[a] Isolated.

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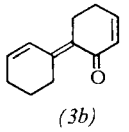
When heated to 50—70 °C in the presence of diethylboryl pivalate, triethylborane and diethyl ketone form *trans*-3-diethylboryloxy-2-pentene *(2a)*; 98% of ethane and only 2% of ethylene are evolved during the reaction (see Table).

Cycloketones having seven or more ring members also react with triethylborane under catalytic conditions to give diethylboryl cycloenolates and hardly any reduction products. Cyclododecanone affords exclusively a mixture of the two *cis/trans* isomers of diethylboryloxycyclododecene. Cycloheptanone, however, gives only 70% of diethylboryloxy-*cis*-cycloheptene alongside 30% of a $C_{14}H_{22}O$ ketone, a condensation product of two ketone molecules.

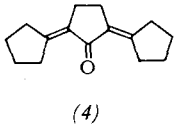
Methyl ketones and particularly acetone, as well as cyclic ketones having five- and six-membered rings (cyclopentanone, cyclohexanone, 2-cyclohexenone), react with triethylborane in the presence of diethylboryl pivalate to give only aldol condensation products. In contrast to the base-catalyzed aldol condensation[3] the yields can be as high as 95%. Compounds that are sensitive to air or to alkalis, *e.g.* the 6-(2-cyclohexenylidene)-2-cyclohexenones *(3a)* and *(3b)*, are also readily obtained. The condensations of cyclopentanone and cyclohexanone proceed particularly rapidly. The dimeric or trimeric condensation products,



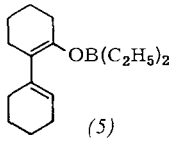
(3a)



(3b)



(4)



(5)

formed according to the molar ratio ketone/triethylborane, are obtained free from boron [*e.g. (4)*] or as diethylboryl enolates [*e.g. (5)*].

(3a) and *(3b)*, as well as, *e.g.*, *(4)*, can also be diethylborylated at 80 °C. Methanolysis quantitatively regenerates the intact boron-free starting materials.

3-Diethylboryloxy-2-pentene (2a):

3-Pentanone (43 g, 0.5 mol) is added dropwise over 80 min 40—60 °C to boiling triethylborane (49 g, 0.5 mol) to which diethylboryl pivalate (2 ml) has been added. Evolution of gas occurs. The reaction mixture is then heated to about 100 °C for about 15 h and 12 l of gas containing (GC) 98% of C_2H_6 and 2% of C_2H_4 is collected. Vacuum distillation gives, after 9 g of fore-run up to 44 °C/15 torr, compound *(2a)* (61 g, 82%), b.p. 57—59 °C/15 torr, containing no other isomer; hardly any residue is left in the distillation flask. IR spectrum (neat liquid): 1680 cm^{-1} ($\nu_{C=C}$); ^{1}H-NMR spectrum (neat liquid): $\tau=5.41$ (vinylic H).

6-(2-Cyclohexylidene)-2-cyclohexenone (3a) and (3b):

2-Cyclohexenone (96 g, 1 mol) is added dropwise at 75 °C over about 6 h to triethylborane (123 g, 1.25 mol) to which diethylboryl pivalate has been added. 28 l of gas comprised of 98% C_2H_6 and 2% of C_2H_4 is liberated. After initial distillation of about 100 g of a mixture (triethyl-

borane and tetraethyl diboroxide) up to 42 °C/14 torr, a yellow liquid (83 g) of b. p. 71—80 °C/0.08 torr is obtained. Methanol (50 ml) is added and all volatile components (bath temperature up to 100 °C, pressure down to 14 torr) are distilled off to yield 74 g (85%) of a pale yellow equimolar mixture of *(3a)* and *(3b)* (GC, ^{1}H-NMR spectrum) of b. p. 73—74 °C/0.09 torr.

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German version: Angew. Chem. *83*, 807 (1971)

[1] *R. Köster, K.-L. Amen, H. Bellut,* and *W. Fenzl,* Angew. Chem. *83*, 805 (1971); Angew. Chem. internat. Edit. *10*, 748 (1971).

[2] *R. Köster* and *W. Fenzl,* Angew. Chem. *80*, 756 (1968); Angew. Chem. internat. Edit. *7*, 735 (1968).

[3] Cf. *A. T. Nielsen* and *W. J. Houlihan,* Org. Reactions *16*, 19, 122 (1968).

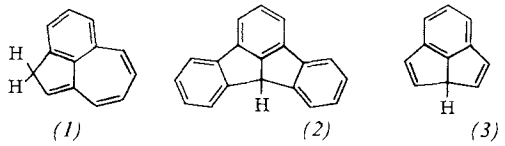
Synthesis of 1*H*-Cyclopent[*cd*]indene and its Anion[**]

By *Peter Eilbracht* and *Klaus Hafner*[*]

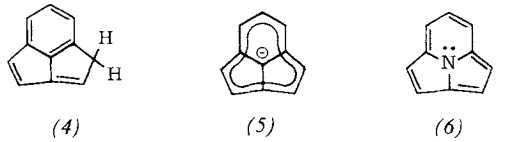
Dedicated to Professor Walter Franke on the occasion of his 65th birthday

In connection with studies of 2*H*-benz[*cd*]azulene *(1)*[1] and the strongly acidic fluoradene *(2)*[2] particular interest[2-6] attaches to the parent system of the latter, 2a*H*-cyclopent[*cd*]indene *(3)* and its 1*H*-isomer *(4)* as well as to their anion *(5)* which is isoelectronic with [3.2.2]cyclazine *(6)*[3].

According to quantum-chemical calculations by *Zahradník et al.*[4], the anion *(5)* containing twelve π-electrons should be electronically more stable than the corresponding cation. *Rapoport et al.*[2] and *Streitwieser Jr.*[6] postulated



(1) *(2)* *(3)*



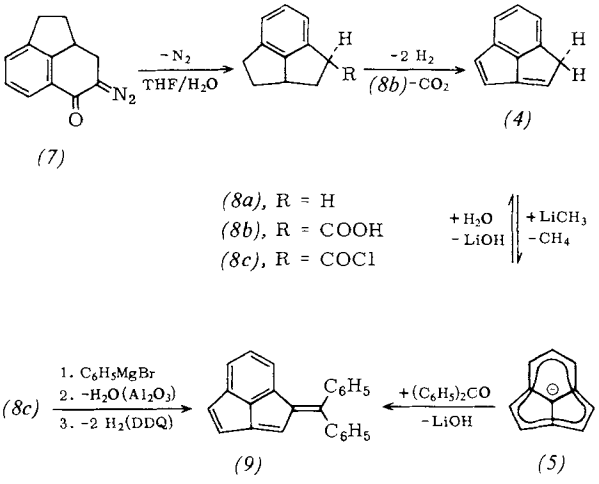
(4) *(5)* *(6)*

that the acidity of 2a*H*-cyclopent[*cd*]indene *(3)* should be comparable with that of phenols. The 1*H*-tautomer *(4)* was not taken into account in these considerations.

In order to test these predictions experimentally we synthesized the lithium salt of *(5)*. *Rapoport et al.*[7] prepared the strained 2,2a,3,4-tetrahydrocyclopent[*cd*]indene *(8a)* and several of its derivatives by Pb salt distillation of 7-carboxy-1-indanacetic acid, but all attempts to introduce double bonds into *(8)* were unsuccessful.

By photolysis of 4-diazo-3,4-dihydro-5(2a*H*)acenaphthenone *(7)*[8] in tetrahydrofuran/water (5:1) with a Hg high-pressure lamp (Q 81, Quarzlampen-Gesellschaft Hanau) we prepared 2,2a,3,4-tetrahydrocyclopent[*cd*]indene-1-carboxylic acid *(8b)*[9] in 36% yield [colorless needles, m. p. 114 °C; UV spectrum (in *n*-hexane): λ_{max} = 217 (3.97), 269 (2.92), 276 (2.90) nm (log ε); NMR spectrum (in CCl_4): τ = −2.42 (1 H/s), 2.30—2.80 (3 H/m), 5.50 (1 H/dd, J = 5 Hz and J = 11 Hz), 6.30—8.50 (7 H/m)].

The acid *(8b)* can be dehydrogenated, with simultaneous decarboxylation, in the gas phase by 10% palladized charcoal at 480 °C in a high vacuum; the hydrocarbon *(4)* produced was isolated at −70 °C and, after chromatography on Al_2O_3 (activity 3, neutral) at −10 °C, was



obtained in 40% yield as a pale yellow oil that solidified at 0 °C and was very sensitive to autoxidation. The UV spectrum of *(4)* in *n*-hexane [λ_{max} = 251 (4.11), 254 (4.11), 273 (3.65), 309 (3.54), 316 (3.64), 330 (3.60) nm (log ε)] is similar to that of 1-isopropylideneindene[10]. The NMR spectrum of *(4)* (in CCl_4) contains, besides a resolved doublet (J = 1.5 Hz) centered at τ = 6.07 for the methylene protons at position 1, two multiplets centered at τ = 3.38 (2 H) and τ = 2.80 (4 H) due to the six further protons. The exclusive formation of *(4)* by the dehydrogenation of *(8b)*—the tautomer *(3)* could not be observed in the product—shows that the fulvenoid hydrocarbon *(4)* has an energy content lower than that of its tautomer 2a*H*-cyclopent[*cd*]indene *(3)*. Attempts to prepare the 1-carboxylic acid of *(4)* directly by *Wolff* rearrangement of 4-diazo-5(4*H*)-acenaphthylenone[11] have so far been unsuccessful.

Contrary to expectation, 1*H*-cyclopent[*cd*]indene *(4)* cannot be converted into its anion *(5)* either by methanolic NaOH or by sodium methoxide in methanol. However, treating *(4)* with methyllithium in tetrahydrofuran/ether (2:1) at −30 °C afforded the lithium salt of *(5)* as a thermally not very stable, red-orange compound, sensitive to autoxidation and hydrolysis, which was precipitated in crystalline form by *n*-hexane. The position and intensity of the long-wave band in the UV spectrum of the Li salt of *(5)* [in THF/ether (20:1) at −30 °C[12], λ_{max} = 338 (3.58), 346 (3.58), 354 (3.60), 458 (2.88) nm (log ε)] are in good agreement with SCF—CI calculations[14]. The NMR

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spectrum (in THF at −55°C) shows, besides the two doublets of the two AB systems of the five-ring protons at $\tau = 3.15$ (H-2, H-3) and 3.65 (H-1, H-4) ($J = 4.0$ Hz), also a multiplet centered at $\tau = 2.70$ for the three six-ring protons. Hydrolysis of *(5)*, which regenerates *(4)*, also confirms the theoretical expectations[4], according to which position 1 or 4 should have a high electron density. In agreement therewith, reaction of *(5)* with benzophenone leads to thermally stable 1-(diphenylmethylene)cyclopent[*cd*]indene *(9)* [yellowish-orange prisms, m. p. 125°C (dec); UV spectrum (in *n*-hexane), $\lambda_{max} = 255$ (4.34), 310 (4.35), 352 (4.28) nm (log ε); NMR spectrum (in CCl_4), $\tau = 2.62$ (6 H/s), 2.66 (3 H/s), 2.70—3.70 (7 H/m)], which can also be obtained from *(8c)*[13] and phenylmagnesium bromide after subsequent dehydration and by dehydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in 30% yield.

Like the formation of *(4)* from *(8b)*, the hydrolysis of the Li salt of *(5)* which leads to *(4)* shows that *(4)* is energetically favored over *(3)*. Correspondingly, a higher total π electron energy was found by SCF—CI calculations[14] for the 1*H*-tautomer *(4)* than for the 2a*H*-tautomer *(3)*[15]. The unexpectedly low acidity of *(4)*, comparable with that of indene, probably represents a considerable difference of 1*H*-cyclopent[*cd*]indene *(4)* from its 2a*H*-tautomer *(3)* for which a p*K* value of 11 has been calculated[6]. This can probably be ascribed to a considerably lower gain of energy on conversion of the fulvenoid tricycle *(4)* into its anion *(5)* than in the corresponding deprotonation of the indene-like hydrocarbon. Also, the correlation obtained by *Streitwieser*'s method between acidity and the π-electron energy difference of anion and hydrocarbon leads to an appreciably lower p*K* value for *(4)* than for *(3)*. Attempts to convert the hydrocarbon *(4)* into its cation and radical are in progress.

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German version: Angew. Chem. *83*, 802 (1971)

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[8] *(7)* was obtained by *M. O. Forster*'s method (J. Chem. Soc. *107*, 260 (1915)) from 3,4-dihydro-4-(hydroxyimino)-5(2a*H*)-acenaphthenone [7] and chloramine as pale yellow, small, light-sensitive rods, m. p. 61°C, in 75% yield.

[9] All the compounds described gave correct analyses.

[10] *A. Pullmann, B. Pullmann, E. D. Bergmann, G. Berthier, Y. Hirshberg*, and *Y. Sprinzák*, Bull. Soc. Chim. France *18*, 702 (1951).

[11] Prepared from 4-amino-5-acenaphthenol hydrochloride (*H. Rapoport, T. P. King*, and *J. B. Lavigne*, J. Amer. Chem. Soc. *73*, 2718 (1951)) and *n*-butyl nitrite; on recrystallization from light petroleum in presence of active charcoal the 4-diazo-5(4*H*)-acenaphthenone first obtained in this synthesis was dehydrogenated to the acenaphthylene derivative; pale yellow needles, m. p. 134°C; yield 56%.

[12] The mean errors in the extinctions, referred to 20°C, in the UV spectrum of the Li salt of *(5)* amount to 5—10%. For UV measurements a solution containing methyllithium was used whose low transmittance below 330 nm did not permit the absorption curve to be observed at lower wavelengths.

[13] Prepared from *(8b)* and thionyl chloride.

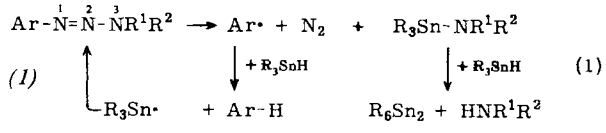
[14] *R. Zahradník*, personal communication.

[15] Simpler HMO calculations for *(3)* and *(4)* led to the same result (*A. Streitwieser, J. I. Brauman*, and *C. A. Coulson*: Supplement Tables of Molecular Orbital Calculations. Pergamon Press, Oxford 1965; *E. Heilbronner* and *P. A. Straub*: HMO Hückel Molecular Orbitals. Springer-Verlag, Berlin—Heidelberg—New York 1966).

Free-Radical $S_H2\gamma$ Diplacement in the Triazene System[**]

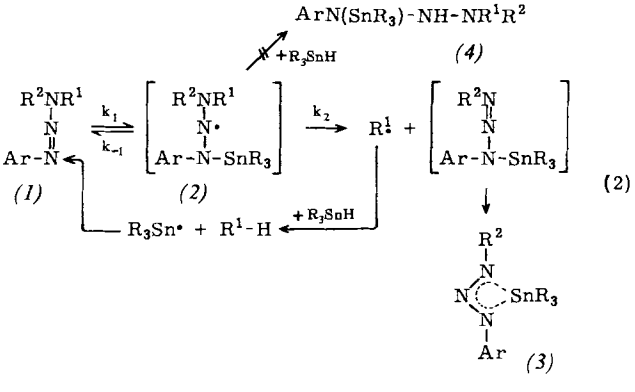
By *Jochen Hollaender* and *Wilhelm P. Neumann*[*]

The action of stannyl radicals $R_3Sn^{\bullet}$ on 1-aryl-3-alkyltriazenes *(1a)—(1c)* resulted in replacement of the arylazo group on N^3 by the stannyl group [eq. (1) and Table]. This $S_H2\alpha$ reaction corresponds to known types of displacement by free radicals[2–5].



(1)

Surprisingly, 1,3-displacement ($S_H2\gamma$) also occurs and predominates or becomes almost the only reaction when at least one of the groups R^1 and R^2 on N^3 forms a stable



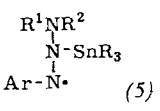
(2)

free radical, *i. e.* when the dissociation energy of its bond to N^3 is lowered. Examples include R^1 = benzyl, triphenylmethyl, or trialkylstannyl [see *(1d)—(1i)*, eq. (2), and Table]. The stannyl radical attacks at N^1. The intermediate

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radical *(2)* rapidly undergoes the reverse reaction (k_{-1}) or elimination (k_2) to give pentacoordinated[6] *N*-stannyltriazene *(3)*. In any case, no stabilization products *(4)*, which could be formed from *(2)* through H-abstraction from the powerful radical scavenger present (organotin hydride), were detected. Attack on N^2 would lead to the intermediate



(5)

radical *(5)*, but no reaction products of this species were observed.

Initial attack by the stannyl radical on N^3 with subsequent 1,1-displacement of R^1 ($S_H2\alpha$) can also be ruled out since

Table. $S_H2\alpha$ and $S_H2\gamma$ reactions of aryltriazenes *(1)* (0.4 M in cumene at 80 °C) with $(C_2H_5)_3SnH$, molar ratio 1:4. Results after six hours' reaction. Catalyst: azoisobutyronitrile.

	(1) Ar	R^1	R^2	Yield (mol.-%) based on reacted *(1)* Ar—H eq. (1)	R^1—H eq. (2)
(a)	C_6H_5	C_2H_5	C_2H_5	100	0
(b)	C_6H_5	$-(CH_2)_5-$		100	0
(c)	p-$CH_3C_6H_4$	CH_3	C_6H_5	100	0
(d)	C_6H_5	$CH_2C_6H_5$	C_6H_5	13	87
(e)	C_6H_5	$CH_2C_6H_5$	$CH_2C_6H_5$	10	90
(f)	C_6H_5	$Sn(CH_3)_3$	$CH_2C_6H_5$	7	91 [a] / $2R^2H$
(g) [b]	C_6H_5	$C(C_6H_5)_3$	C_6H_5	7 [c]	93
(h)	C_6H_5	$Sn(CH_3)_3$	C_6H_5	2	98 [a]
(i) [d]	C_6H_5	NH_2	C_6H_5	61	[e]

[a] R^1—H is in equilibrium with *(1f)* or *(1h)* respectively.
[b] At 60 °C without catalyst.
[c] Benzene (Ar—H) is formed here from spontaneous decomposition of *(1g)*.
[d] In toluene at 20 °C without catalyst.
[e] NH_3 is formed. A quantitative determination has yet to be performed.

benzylaniline, diphenylbenzylamine, or *N*-benzylimidazole gives no toluene under the above conditions. Moreover, such an attack is unlikely in the case of the triphenylmethyl derivative *(1g)* for steric reasons.

It may be assumed that attack of the π system of the azo group also occurs as a competing reaction in the case of eq. (1) but remains very much in the background owing to a lack of readily replaceable groups R. This behavior of the N=N group would correspond to that of internal C=C groups[7].

The reactions depicted in eq. (1) and eq. (2) are greatly accelerated, or in some cases even made possible, at 80 °C by free radicals from azoisobutyronitrile or at 28 °C by UV irradiation (λ_{max} 254 nm).

The triazene system behaves here as a triaza analog of the allyl system and it is likely that the $S_H2\gamma$ reaction described above is possible with all allyl analogs, as we have actually observed with the allyl system itself[8]. A number of allyl displacement reactions proceed by the same mechanistic route[9], while various other free radical reactions[10] correspond to an $S_H2\beta$ mechanism.

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An α-Lactam Derived from 2-Adamantylamine[**]

By *Erach R. Talaty, James P. Madden*, and *Louis H. Stekoll*[*]

Several α-lactams having a *tertiary*-alkyl group attached to the nitrogen atom are known[1]. Attempts to prepare α-lactams with other types of alkyl substituents on nitrogen have been made, but such α-lactams have been reported to be either not formed or too reactive to be isolated[2]. We now report the isolation of an α-lactam, 1-(2-adamantyl)-3-(1-adamantyl)aziridin-2-one *(2a)*, which has a *secondary*-alkyl group attached to position 1, and is remarkably stable. Compounds of this type could also have potential applications in medicinal chemistry, since 1-adamantylamine and its derivatives have been reported to have antiviral activity[3].

R^1—CHR^2—CO—R^3 *(1)*
(a), R^1 = 1-adamantyl, R^2 = H, R^3 = Cl
(b), R^1 = 1-adamantyl, R^2 = Br, R^3 = Cl
(c), R^1 = 1-adamantyl, R^2 = Br, R^3 = NH-2-adamantyl

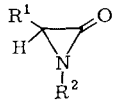
The acid chloride *(1a)* was treated with bromine in boiling carbon tetrachloride until conversion into *(1b)* was complete, and the crude reaction mixture was allowed to react with 2-adamantylamine to afford, in 71% over-all yield, the bromo-amide *(1c)*, m.p. 237.5—240.0 °C (decomp.) [NMR ($CDCl_3$, 60 MHz, δ-value in ppm relative to TMS): 6.60 (N—H/broad d, J = 8 Hz), 4.08 (1 H/s), 4.08 (1 H/broad d, J = 8 Hz), 2.26—1.44 (29 H/m); mass spectrum: *m/e* 407/405 (M^+), 326 (M^+—Br)]. Reaction of *(1c)* with potassium *tert*-butoxide in ether at 0 °C effected ring closure to the desired α-lactam *(2a)*, m.p. ≈225 °C (decomp.). However, in contrast with the preparation of α-lactams such as *(2b)*[4], where the ring-closure could be

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[8] *H.-J. Albert, W. P. Neumann*, and *H.-P. Ritter*, Liebigs Ann. Chem. *737*, 152 (1970).
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[10] *J. K. Kochi* and *P. J. Krusic*, J. Amer. Chem. Soc. *91*, 3944 (1969), and further literature cited therein.

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driven to completion by the use of an excess of base without the concomitant formation of other products, the present reaction required very careful control of the reagents and experimental conditions in order to achieve optimum conversions. The isolation of *(2a)* was accomplished only after fractional crystallization at low temperatures. The structure of *(2a)* is supported by spectral data [IR (CCl_4): $\nu \approx 1850\,cm^{-1}$; NMR ($CDCl_3$, 60 MHz, δ-value in ppm relative to TMS): 2.53 (H^3/s), 3.16 (1 H/broad s), *ca.* 2.4—1.4 (29 H/m); mass spectrum: *m/e* 325 (M^+)].



(2)

(a), R^1 = 1-adamantyl, R^2 = 2-adamantyl
(b), $R^1 = R^2$ = 1-adamantyl
(c), $R^1 = C_6H_5$, $R^2 = C(CH_3)_3$
(d), $R^1 = R^2$ = *tert*-alkyl

The thermal stability of the novel α-lactam *(2a)* is illustrated by the observation that its complete decomposition in boiling xylene (138 °C) at a concentration of 0.4 mmol/6 ml requires 1 h, whereas the complete decomposition of *(2b)* under the same conditions requires 3.5 h. The chemical stability of *(2a)* is equally remarkable: its complete decomposition in boiling methanol at a concentration of 1.5 mmol/10 ml occurs only after 1.75 h. By comparison, *(2b)* requires 30 h for complete decomposition under identical conditions, and *(2c)* is reported to decompose in methanol at 5 °C within 20 minutes[5]. Thus, the stability of *(2a)* is superior to that of *(2c)*[6] and approaches that of *(2d)*, the most stable class of α-lactams known so far.

Received: July 5, 1971 [Z 471 IE]
German version: Angew. Chem. *83*, 848 (1971)

[1] See *E. R. Talaty* and *C. M. Utermoehlen*, Tetrahedron Lett. *1970*, 3321, and references cited there; *J. C. Sheehan* and *M. M. Nafissi-V*, J. Org. Chem. *35*, 4246 (1970); *S. Sarel, B. A. Weissman*, and *Y. Stein*, Tetrahedron Lett. *1971*, 373.

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[6] The published data on the thermal stability of *(2c)*—appreciable decomposition at 105 °C—do not allow an accurate comparison with *(2a)* and *(2b)*; *J. J. Fuerholzer*, Ph. D. dissertation, University of Nebraska, 1965.

CONFERENCE REPORTS

Reactions of Adamantanes and Their Derivatives in Sulfuric Acid

By *J. Schlatmann*[*]

Under suitable conditions 1-adamantanol can be converted into adamantanone in concentrated sulfuric acid. The key reaction is the reversible isomerization of 1- to 2-adamantanol; the equilibrium is much in favor of the 1-isomer. It has been proved that this isomerization occurs intermolecularly. The 2-adamantanol present in the reaction mixture is transformed into adamantanone by a hydride shift, the hydride acceptor being either the adamantanyl cation (yielding adamantane as a by-product) or the sulfuric acid. Adamantane is reconverted into 1-adamantanol by sulfuric acid; thus the synthesis of adamantanone can also be carried out from adamantane (yield *ca.* 50%).

Besides adamantanone, adamantanediols are formed from 1-adamantanol in sulfuric acid, presumably also in hydride shift reactions, with either the adamantanyl cation or the sulfuric acid as hydride acceptor. Although these are unimportant side products when the reactions are performed in concentrated sulfuric acid, conditions can be found in which the diol formation will be enhanced and the adamantanone formation suppressed because all these reactions are influenced differently by the concentration of the sulfuric acid. Thus in 20% fuming sulfuric acid the formation of the 1,3-, 1,4- and 2,6-adamantanediols predominates. After oxidation with chromic acid the components of the reaction mixture can be separated and 5-hydroxyadamantanone (yield *ca.* 50%) and 2,6-adamantanedione can be isolated in pure form.

Lecture at Aachen on May 25, 1971 [VB 309 IE]
German version: Angew. Chem. *83*, 732 (1971)

[*] Dr. J. Schlatmann
N. V. Philips-Duphar
Weesp (Holland)

Mechanism of Cyanation of Tertiary Amines[**]

By *Gabor Fodor* and *Shiow-yueh Abidi*[*]

We have been able to show that the von Braun cyanogen bromide degradation of tertiary amines proceeds by two successive steps:

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[**] This work is being supported by National Science Foundation, Grant GP-26558.

1. Electrophilic addition of a cyano group to nitrogen, giving an *N*-cyano ammonium salt in a reaction that is immeasurably fast even at −60 °C.

2. Attack by the bromide ion on a carbon atom attached to nitrogen, giving a cyanamide and RBr in a reaction whose rate is measurable between −30 and −9 °C.

NMR measurements on 1-cyano-*trans*-decahydro-1-methylquinolinium bromide show the second stage to be a reaction of the first order; it occurs ten times faster in $CDCl_3$ than in CD_3CN. The activation energy of decomposition amounts to 18 kcal/mol. On replacement of the bromide by a less nucleophilic (or non-nucleophilic) anion, *e.g.*, hexachloroantimonate, methanesulfonate, *p*-toluenesulfonate, or tetrafluoroborate, stable quaternary *N*-cyano ammonium salts can be isolated for the first time, analyzed, and subjected to examination of their chemical behavior.

Recently also we have been able to trap the adduct formed from methyl chloroformate and *trans*-decahydro-1-methylquinoline at low temperature and to stabilize it as fluoroborate.

To determine the stereochemistry of the *N*-isomeric products obtained we have separated them as fluoroborates and are presently studying (a) their nuclear Overhauser effect at 250 MHz and at 100 MHz, (b) their ^{13}C-NMR spectra, and (c) the structure of the major product by X-ray methods.

Lectures at Darmstadt on May 26, 1971, München on June 4, 1971, and at Erlangen on June 7, 1971 [VB 310 IE]
German version: Angew. Chem. *83*, 732 (1971)

Synthesis and Structure of Haloamines

By *Jochen Jander, Klaus Knuth, Rolf Minkwitz*, and *Werner Renz*[*]

The lecture concerned, *inter alia*, the synthesis and solid-state FIR-spectroscopic study of the structure of $NI_3 \cdot 3NH_3$ *(1)*, the so-called $NH_2I \cdot NH_3$ *(2)*, the so-called NH_2I *(3)* [better formulated, in view of the results below, as $NI_3 \cdot \sim 5NH_3$ *(2)* and $NI_3 \cdot \sim 2NH_3$ *(3)*, respectively] as well as of the *N*-iodomethylamines $CH_3NI_2 \cdot CH_3NH_2$ *(4)*, $CH_3NI_2 \cdot Py$ *(5)*, $CH_3NI_2 \cdot (CH_3)_3N$ *(6)*, CH_3NI_2 *(7)*, and $(CH_3)_2NI$ *(8)*. The NI_3 adducts were obtained by treatment of ICl or I_2 with NH_3 in aqueous solution or with liquid NH_3; $(NI_3 \cdot NH_3)_n$ can be used as iodinating agent, as well as ICl or I_2, for preparation of the *N*-iodomethylamines[1]. Because of their sensitivity, compounds *(1)*—*(4)* and *(7)*—*(8)* can be studied only at low temperatures; this was possible by use of a new low-temperature measurement technique.

The glittering green *(1)*, the pale red *(2)*, and the black *(3)* contain the same polymeric structure as $(NI_3 \cdot NH_3)_n$ consisting of NI_4 tetrahedra joined by common iodine atoms[2–4]; differences were found as follows:

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(1) and *(2)* bind more NH_3 than $(NI_3 \cdot NH_3)_n$ and, because the contact sites are occupied by NH_3, they contain no I—I contacts between the tetrahedron chains as $(NI_3 \cdot NH_3)_n$ does; *(2)* and *(3)*[5] are amorphous to X-rays and thus contain only ill-developed and possibly shorter tetrahedron chains than $(NI_3 \cdot NH_3)_n$.

The reddish-yellow *(4)*, the brick-red *(5)*, the orange *(6)*, and the reddish-brown *(7)* are also polymeric and consist of NI_3C tetrahedron chains which either, as in *(7)*, use the iodine atoms that are not part of the chain for binding by I—I contacts or, as in *(4)*—*(6)*, for binding the nitrogen base. This result has been confirmed for *(5)* by X-ray investigations.

The yellow *(8)* is probably monomeric; two very long-wave FIR bands $< 100\ cm^{-1}$ can be interpreted either as lattice vibrations or as very weak intermolecular N—I contacts, *i.e.* as a precursor of a stable tetrahedron chain.

Lecture at Aachen on June 8, 1971 [VB 311 IE]
German version: Angew. Chem. *83*, 767 (1971)

[1] *J. Jander, U. Engelhardt*, and *G. Weber*, Angew. Chem. *74*, 75 (1962); Angew. Chem. internat. Edit. *1*, 46 (1962).

[2] *J. Jander, L. Bayersdorfer*, and *K. Höhne*, Z. Anorg. Allg. Chem. *357*, 215 (1968).

[3] *H. Hartl, H. Bärnighausen*, and *J. Jander*, Z. Anorg. Allg. Chem. *357*, 225 (1968).

[4] *K. Knuth, J. Jander*, and *U. Engelhardt*, Z. Naturforsch. *24b*, 1476 (1969).

[5] *J. Jander* and *U. Engelhardt*, Z. Anorg. Allg. Chem. *339*, 225 (1965).

Molten Salts at High Pressures and High Temperatures

By *Klaus Tödheide*[*]

The macroscopic properties of molten salts cannot yet be calculated from the properties of the ions and molecules by means of statistical mechanics. Thus models for molten salts have been developed in order to enable interpretations of experimental results as well as predictions, where experimental information is missing. For the purpose of testing the capability of these models to describe the density dependence of macroscopic properties of molten salts correctly, experiments at high pressures are necessary. It is only in recent years that the first investigations of this type have been performed.

The specific conductivity of the molten alkali metal nitrates has been measured up to 60 kbar. In the region of low and medium pressures (for $NaNO_3$ up to about 20 kbar) straight lines were obtained for the logarithm of the specific conductivity as a function of pressure and as a function of the reciprocal absolute temperature. From the slopes of these lines, and from experimentally determined PVT data, the activation volumes and activation energies for the equivalent conductivity have been calculated. The activation volume increases from $0.7\ cm^3/mol$ for $LiNO_3$ to $8.0\ cm^3/mol$ for $CsNO_3$, while the isochoric activation energy decreases from 3.5 to 1.4 kcal/mol. The ratio of the isochoric to the isobaric activation energy decreases from 0.97 for $LiNO_3$ to 0.36 for $CsNO_3$. This result indicates

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that for the charge transport process at constant pressure very little energy is required for the volume expansion in $LiNO_3$, whereas with $CsNO_3$ almost two thirds of the total isobaric activation energy is needed for this purpose.

The experimental results cannot be interpreted quantitatively in terms of any of the molten salt models. They are, however, in qualitative agreement with the "density fluctuation hole" model developed by *Fürth*. In this model the formation of holes of about the size of the ions by density fluctuations has a dominating influence on the rate determining step of the charge transport process.

If the molten alkali metal nitrates are compressed to densities higher than that of the corresponding solid phase, the activation volume decreases over a small pressure range to half its original value, whilst the activation energy increases considerably. The transition occurs at about 22 kbar for $NaNO_3$ and as low as at about 14 kbar for KNO_3, but was not observed in the whole pressure range covered for $LiNO_3$ with its relatively small cation. This result also agrees with the "hole" model, since at such high densities no holes are formed which are sufficiently large for the bigger ions.

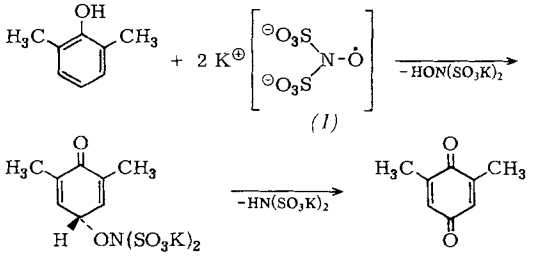
For glass-forming molten salts the models of *Cohen* and *Turnbull* and of *Adam* and *Gibbs* are better suited to describe the pressure and temperature dependence of the electrical conductivity, especially in the low temperature range.

At supercritical temperatures, where the density can continuously be varied from that of a dilute gas to that of a liquid, the transition from a non-conducting vapor to an ionically conducting dense fluid phase may be investigated as a function of the average distance between the particles at constant temperature. This has been done by measuring the specific conductivity and the density as functions of pressure and temperature. Measurements on $BiCl_3$, whose critical temperature is 905 °C, demonstrated that the molar conductivity increases with density by four to five orders of magnitude mostly within a narrow interval around the critical density.

Lecture at Göttingen (Germany) on June 10, 1971 [VB 312 IE]
German version: Angew. Chem. *83*, 768 (1971)

SELECTED ABSTRACTS

Oxidations with potassium nitrosodisulfonate (*Fremy*'s radical) *(1)* are summarized by *H. Zimmer, D. C. Lankin,* and *S. W. Horagen. (1)* is a specific oxidizing agent that converts phenols and secondary amines into quinones. With more complicated structures such as indole and carbazole derivatives, quinone formation is accompanied



by dehydration and coupling. [Oxidations with Potassium Nitrosodisulfonate (*Fremy*'s Radical). The Teuber Reaction. Chem. Rev. *71*, 229—246 (1971); 84 references, 11 tables, numerous formulas]

[Rd 386 IE -M]

Direct liquid-phase fluorination of organic compounds is reviewed, with particular reference to the author's own studies, by *V. Grakauskas.* A discussion of experimental technique is followed by examples of fluorination of organic nitrogen compounds (ureas, carbamates, guanidine derivatives, amides), alkali metal salts, aliphatic nitro compounds, primary nitramines, and carboxylic acids in aqueous solution and aromatic hydrocarbons. [Direct Liquid Phase Fluorination of Organic Compounds. Intra-Science Chem. Reports *5*, 85—104 (1971); 94 references, numerous formulas]

[Rd 387 IE -M]

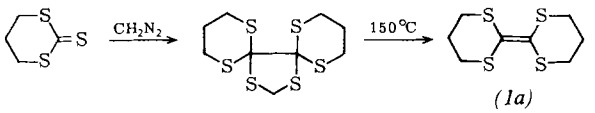
Properties and uses of trifluoroacetic anhydride constitute the subject matter of an article by *R. E. A. Dear.* Space is devoted to physical and chemical properties such as esterification, trifluoroacetylation, electrophilic substitution of aromatic compounds, as well as acylation of aliphatic compounds with trifluoroacetic anhydride, rearrangements promoted by trifluoroacetic anhydride, and a number of other reactions of trifluoro- and chlorodifluoroacetic anhydride. The report closes with safety measures recommended for handling the reagent and toxicity data. [Trifluoroacetic Anhydride: Properties and Uses. Intra-Science Chem. Reports *5*, 37—53 (1971); 118 references, numerous formulas]

[Rd 388 IE -M]

New syntheses of organic sulfur compounds suitable for industrial use are considered by *F. Becke* in a review article. Particular attention is devoted to the reactions of sulfur with organic halo compounds: Reactions with hexachlorocyclohexane; mechanism of the "sulfur reaction"; reactions with aliphatic chlorides, with phosphorus-nitrogen compounds, and with benzisothiazoles; formation of heterocyclic compounds containing no sulfur is also mentioned. [New Syntheses of Organic Sulfur Compounds which Are Suitable for Industrial Purposes. Internat. J. Sulfur Chem. *6*, 77—83 (1971); 19 references, formulas]

[Rd 389 IE -M]

Synthetic routes to tetrathioethylenes *(1)*, and especially the highly effective new technique of orthothiooxalate pyrolysis, represent the body of a review by *D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garret,* and *N. D. Canfield.* The electrochemical properties of characteristic tetrathioethylenes were also studied. The UV spectra of these compounds can be explained by EHT calculations



(1a)

including 3d orbitals of the sulfur. The chemistry of *(1)* deviates from that of "electron-rich olfins". Syntheses *via* carbenes are also successful. [Tetrathioethylenes. J. Amer. Chem. Soc. *93*, 2258—2268 (1971); 70 references, numerous formulas]

[Rd 390 IE -M]

Kinetic data for abstraction of hydrogen and deuterium by methyl and trifluoromethyl radicals in the gaseous phase have been collected by *P. Gray, A. A. Herod,* and *A. Jones.* The reaction can be represented formally by

$$R + XH \longrightarrow RH + X$$
$$R + XD \longrightarrow RD + X$$

R = methyl, trifluoromethyl; X = free radical or atom

The review encompasses: Experimental methods and elementary theoretical considerations; abstraction from H_2, HD, D_2, from CH and CD, NH and ND, OH and OD, and SH and SD bonds, as well as from members of isoelectronic series; attack by free radicals at specific positions of the molecule; comparison of reactivity of methyl and trifluoromethyl radicals; and isotope effects in abstraction reactions. [Kinetic Data for Hydrogen and Deuterium Atom Abstraction by Methyl and Trifluoromethyl Radicals in the Gaseous Phase. Chem. Rev. *71*, 247—294 (1971); 230 references, 48 tables, numerous formulas]

[Rd 392 IE -M]

Photoelectron spectroscopy in chemistry is the subject of a report by *S. D. Worley.* This new technique is based upon measurement of the energies of photoelectrons emitted by molecules on irradiation with ultraviolet light. A review of theoretical principles is followed by a discussion of the photoelectron spectra of many polyatomic molecules. Examples include alkanes, alkenes, alkynes, cyclic hydrocarbons, azabenzenes and azanaphthalenes, metal carbonyl compounds, furans, pyrroles, thiophenes, amines, hydrazines, alcohols, aldehydes, ketones, acids, ethers, and oxides, as well as compounds containing B, P, As, and S. [Photoelectron Spectroscopy in Chemistry. Chem. Rev. *71*, 295—314 (1971); 187 references, 2 tables, numerous formulas]

[Rd 393 IE -M]

Syntheses and chemical properties of heterocyclic systems bearing phosphorus substituents are summarized by *Derek Redmore* in a review covering the topic up to September 1970. The compounds considered contain phosphorus bonded to a C atom of the heterocyclic system. In the light of general synthetic methods, the author discusses nucleophilic displacements on the phosphorus by heterocyclic organometallic compounds, nucleophilic displacements by phosphorus nucleophiles, nucleophilic addition reactions, cycloaddition reactions, condensation reactions, free-radical reactions, as well as electrophilic substitution by phosphorus. [Heterocyclic Systems bearing Phosphorus Substituents. Synthesis and Chemistry. Chem. Rev. *71*, 315—337 (1971); 154 references, 12 tables, numerous formulas]

[Rd 394 IE -M]

Reaction of carboxylic esters with sodium in presence of trimethylchlorosilane *(1)* in inert solvents is reviewed by *K. Rühlmann.* Compound *(1)* traps all basic products of Bouveault-Blanc condensation so that the reaction mixture remains neutral and base-catalyzed side reactions (β-elimination, Claisen and Dieckmann condensation) no longer occur. The bis(siloxy)alkenes *(2)* formed by C—C linkage can be isolated, converted into acyloins by acid hydrolysis or alcoholysis, or used *in situ* for further reactions. Alkoxysilanes such as *(3)* occur as minor products.

$$2\ R^1\text{-}COOR^2 + 4\ Na + 4\ Cl\text{-}SiMe_3 \longrightarrow$$
(1)

$$R^1\text{-}C(\text{=}C\text{-}OSiMe_3)\text{-}R^1 + 2\ R^2\text{-}OSiMe_3 + 4\ NaCl$$
(2) *(3)*

Dicarboxylic esters afford 1,2-bis(siloxy)-1-cycloalkanes instead of *(2)*. [Die Umsetzung von Carbonsäureestern mit Natrium in Gegenwart von Trimethylchlorsilan. Synthesis *1971*, 236—253; 125 references, 14 tables, numerous formulas]

[Rd 395 IE -M]

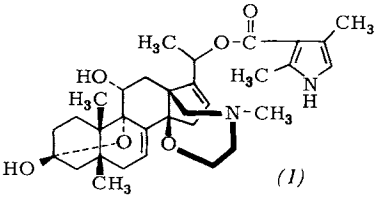
Chemistry of optically active sulfur compounds having S as active center are dealt with in a review by *A. Nudelman.* The article embraces sulfoxides (stereospecific synthesis, resolution, racemization, spectral studies, reactions, steroidal and penicillin sulfoxides), sulfinates, sulfonium salts, sulfonium ylides, oxosulfonium methylides, complex sulfonium salts, sulfinamides, sulfilimines, sulfoximines, sulfites, thiosulfinates, sulfinimidoates, sulfinimide amides, sulfonimide amides, [^{16}O, ^{17}O]sulfones and -sulfonates, as well as sulfinic acids. [The Chemistry of Optically Active Sulfur Compounds. Internat. J. Sulfur Chem. *6*, 1—39 (1971); 234 references, numerous formulas]

[Rd 396 IE -M]

Stereochemistry of organic sulfur compounds is reviewed by *K. K. Anderson.* Since the S atom can accommodate up to six ligands and 12 electrons in its valence shell, the possible structures are legion. Examples of tricoordinate S^{IV} compounds include sulfonium salts, sulfoxides, and sulfilimines. Representatives of tetracoordinate S^{VI} compounds are sulfones and sulfoximines. [Stereochemistry of Organic Sulfur Compounds. Internat. J. Sulfur Chem. *6*, 69—76 (1971); 56 references, numerous formulas]

[Rd 397 IE -M]

Chemistry and pharmacology of batrachotoxin *(1)*, a steroidal alkaloid from the poison arrow frog *Phyllobates aurotaenia,* is reviewed by *E. X. Albuquerque, J. W. Daly,* and *B. Witkop.* Compound *(1)* exerts novel, selective effects on electrogenic membranes. In many cases the action can be explained in terms of an irreversible increase in permeability to Na^+ ions. The subsequent reactions promoted by *(1)* can be blocked reversibly by tetrodo-



(1)

toxin. [Batrachotoxin: Chemistry and Pharmacology. Science *172*, 995—1002 (1971); 33 references, 3 tables, 9 figures]

[Rd 398 IE –M]

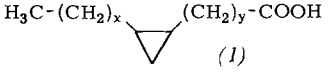
Monosubstituted diazenes (diimides) R—N=NH are considered by *E. M. Kosower*, particular attention being paid to the author's own studies. The chemical possibilities presented by monosubstituted diazenes will become clear in further work. Diazenes are reactive, readily accessible intermediates that can decompose, *inter alia*, *via* free radicals or carbanions. The article embraces: Synthesis (by fragmentation, decarboxylation, ester elimination, aldehyde elimination, oxidation, reduction); physical and chemical properties; bimolecular reactions; chemical and biological significance of diazenes. [Monosubstituted Diazenes (Diimides). Surprising Intermediates. Accounts Chem. Res. *4*, 193—198 (1971); 44 references, 3 tables, numerous formulas, 1 figure]

[Rd 399 IE –M]

Comparative pharmacology of indole alkaloids and their derivatives, which act upon the cerebral blood circulation and the metabolism of nervous tissues, is surveyed by *M. Aurousseau*. The compounds are of considerable importance in the treatment of the steadily increasing number of cases of damage to cerebral blood vessels. The author deals with the following groups of compounds: Rauwolfia alkaloids (reserpine group, ajmalicine group); ergot alkaloids; *Vinca minor* alkaloids (vincamine). [Pharmacologie comparée des alcaloides indoliques et de leur dérivés agissant sur la circulation cérébrale et le métabolime de tissu nerveux. Chimia therapeutica *6*, 221—234 (1971); 104 references, 16 tables and figures]

[Rd 400 IE –M]

Biosynthesis of cyclopropane rings is summarized by *J. H. Law*. Naturally occurring fatty acids *(1)*, amino acids, terpenes, and sterols containing cyclopropane rings have all become known. The CH_2 unit which forms the three-membered ring with a C=C double bond comes from *S*-adenosylmethionine. Cyclopropane synthetase from *Clostridium butyricum* catalyzes the biosynthesis of fatty acids

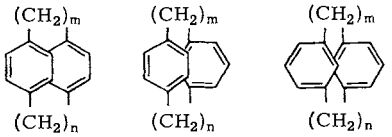


(1)

having cyclopropane rings; a phosphatidylethanolamine was found to be a good substrate. [Biosynthesis of Cyclopropane Rings. Accounts Chem. Res. *4*, 199—203 (1971); 45 references, 2 tables, selected formulas]

[Rd 401 IE –M]

Recent studies on [*m.n*]cyclophanes are discussed by *D. J. Cram* and *J. M. Cram*, particular emphasis being placed on systems having m and $n \leq 3$. These compounds *(1)*—*(3)* (para-, metapara-, and metacyclophane) differ considerably from their open-chain analogs. Bent benzene rings and abnormally small ring-ring distances number among the



(1) *(2)* *(3)*

characteristic features of these highly strained molecules. The consequences of this structure include sterically hindered rotation of the rings, transannular effects, and unexpected chemical reactions. [Cyclophane Chemistry: Bent and Battered Benzene Rings. Accounts Chem. Res. *4*, 204—213 (1971); 41 references, numerous formulas]

[Rd 402 IE –M]

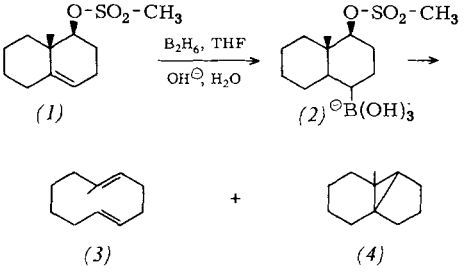
Paramagnetic probes for NMR relaxation studies of phosphoryl transfer enzymes are reported by *M. Cohn* and *J. Reuben*. The technique is made possible by the fact that enzymatic reactions of nucleoside triphosphates of the type

$$ATP^{4-} + XH \rightleftharpoons ADP^{3-} + XPO_3^{2-} + H^+$$

require divalent metal ions that can be replaced, *e.g.*, by the paramagnetic Mn^{2+} ion. NMR relaxation and ESR studies of this kind reveal quantitative information about configuration and dynamics of the active site of an enzymatic system in solution which could not be obtained otherwise. [Paramagnetic Probes in Magnetic Resonance Studies of Phosphoryl Transfer Enzymes. Accounts Chem. Res. *4*, 214—222 (1971); 54 references, 5 figures, 1 table]

[Rd 403 IE –E]

The synthesis of 1,5-dienes and 1,5- and 1,6-cyclodecadienes by solvolytic cleavage of intermediate borinic acid derivatives such as *(2)* is reviewed by *J. A. Marshall*. Particular attention is devoted to 1,5-dienes that participate, *e.g.*, in



(1) *(2)* *(3)* *(4)*

the biosynthesis of terpenes. Conversion of the sulfonate *(1)* by diborane into the product *(2)*, which is subsequently subjected to alkaline solyolysis to give 1-methyl-1,5-cyclodecadiene *(3)* and the tricyclic compound *(4)* (97:3), represent a typical example. [Diene Synthesis *via* Boronate Fragmentation. Synthesis *1971*, 229—235; 31 references, 1 table, numerous formulas]

[Rd 405 IE –L]

Electroorganic synthesis is the topic of a review by *S. Wawzonek*. Anions, radical anions, radicals, radical cations, and carbonium ions can be produced from organic compounds by direct electron transfer; these species can then react with one another, with the solvent, with the electrodes, or with added compounds to form isolable products. A brief introduction to theory and a description of equipment are followed by numerous examples of applications supplemented by experimental procedures. [Electroorganic Syntheses. Synthesis *1971*, 285—301; 137 references, 5 figures, 1 table, numerous formulas]

[Rd 406 IE –L]

The spectra of simple molecular ions in the gaseous phase are surveyed by *G. Herzberg*. Spectra of this kind permit an insight into the electronic structure, and thus into the bonding, of the corresponding neutral molecules. Experimental methods for production of molecular ions are considered first, and their emission, absorption, photoelectron, and fluorescence spectra are then discussed. Molecular ions have also been detected in planetary atmospheres and in interstellar gas. [Spectra and Structure of Molecular Ions. Quart. Rev. Chem. Soc. *25*, 201—222 (1971); 52 references, 23 figures]

[Rd 407 IE–K]

NMR studies of molecular relaxation processes in solid polymers are described by *D. W. McCall*. A discussion of theoretical principles is followed by a wealth of examples of applications. Thus the method can be used to follow the movements of several different side chains, special movements of the main chain in crystalline polymers, and processes occurring near the glass transition temperature. [Nuclear Magnetic Resonance Studies of Molecular Relaxation Mechanisms in Polymers. Accounts Chem. Res. *4*, 223—232 (1971); 46 references, 17 figures]

[Rd 404 IE–E]

BOOK REVIEWS

Catalytic Processes and Proven Catalysts. By *C. L. Thomas*. Academic Press, New York—London 1970. xiii, 284 pp., 19 tab., bound, $ 12.50.

Thanks to his long years of service as a scientific advisor to the Sun Oil Company, the author has a wealth of experience in the operation of commercial catalytic processes. He has now done us the service of setting this experience down in book form, for the first time making publicly available proprietary information which in many cases was previously jealously guarded.

The book includes descriptions of a large number of catalytic reactions, arranged by reaction type. They include oxidation, hydrogenation, dehydrogenation, dehydration, alkylation, isomerization, cracking and reforming, polymerization, ammonia and methanol synthesis, synthesis gas and hydrogen production, and gas purification processes. Proven catalysts are described for each reaction, and their advantages and disadvantages are discussed; commercial catalysts are also described, but only those from American manufacturers. In addition, the book contains data on the most favorable operating conditions, particularly temperature and concentrations, the space-velocity, and the catalyst lifetime. There is also information on the various types of reactors, the handling of catalysts, catalyst poisons, and the regeneration (especially by eliminating carbon deposits) of inactivated catalysts. In conclusion, there is a section on carriers.

The book is not intended as a textbook, but it can be used as a guide or collection of formulations, which should be particularly pleasing to practising chemists and chemical engineers, who will find it a valuable aid in the solution of catalyst problems.

E.-G. Schlosser [NB 989 IE]

Catalyst Handbook. Wolfe Scientific Books, London 1970. 1st ed., 231 pp., 81 figs., 16 tab., £ 3.15.

This book, specifically concerned with unit processes encountered in the manufacture of ammonia and hydrogen, deserves attention for two reasons. In the first place, it contains a number of full yet concise explanations of the fundamentals of heterogeneous catalysis, which justifies its description as a "handbook". But secondly, and what is more important, it aims to provide the catalyst user with a wealth of important practical information, all of which was specifically obtained on the range of catalysts distributed by ICI.

Many well-known scientists, including *S. P. S. Andrew*, *G. W. Bridger*, *J. S. Campbell*, *G. C. Chinchen*, *P. Craven*, *D. A. Dowden*, *D. R. Goodman*, *J. J. Phillipson*, *C. B. Snowdon*, *W. Spendley*, and *P. W. Young*, have collaborated in the preparation of this book. The questions of catalyst activity, selectivity, and lifetime, of decisive importance in all processes, are dealt with thoroughly by all the authors, and run as an underlying theme throughout the book. The specific reactions described are the desulfurization of hydrocarbons, hydrocarbon-reforming, removal of carbon monoxide, and ammonia synthesis. In each case the various methods used, the selection of catalyst, the reaction mechanism, and the kinetics are described; mention is also made of problems concerned with the need to use certain feedstock blends and to control catalyst poisons. One section is devoted to the testing and another to the practical handling of catalysts. In addition, computer programs for converter calculations are included. An extensive tabular appendix contains data on ICI catalysts, substance properties, and gas-phase equilibrium constants, together with examples of calculations.

This book is an important reference work for the plant designer and chemical engineer and is highly recommended.

E.-G. Schlosser [NB 988 IE]

Technique of Organic Chemistry. Edited by *A. Weissberger*. Vol. IX/Part 2: Microwave Molecular Spectra. By *W. Gordy* and *R. L. Cook*. Interscience, New York 1970, 2nd Edit., 747 pp., bound, *ca.* DM 139.—[1].

In recent years, microwave spectroscopy has progressed in measuring technique, theory, and evaluation technique to such a degree that this method is applicable to a series of problems that face the chemist. It provides the most precise geometrical data on molecules, allows the study of conformation equilibria, rearrangements, and short-lived intermediates, is suitable for qualitative and quantitative analyses, and provides information about the electronic structure. Microwave spectroscopy was formerly

[1] Cf. Angew. Chem. internat. Edit. *6*, 1092 (1967).

discussed in "Weissberger" in short chapters (*Gordy*, 1956; *Dailey*, 1960); an entire volume is now devoted to this method. It is a revised version of a book by *Gordy*, *Smith*, and *Trambarulo*, which was published by Wiley in 1953.

Contents: Introduction, Theoretical Aspects of Molecular Rotation; Microwave Transitions – Line Intensities and Shapes; Diatomic Molecules; Linear Polyatomic Molecules; Symmetric-Top Molecules, Asymmetric-Top Molecules; Centrifugal Distortion; Nuclear Hyperfine Structure in Molecular Rotational Spectra; Effects of Applied Electric Fields; Effects of Applied Magnetic Fields; Internal Rotation; Derivation of Molecular Structures; Quadrupole Couplings, Dipole Moments, and the Chemical Bond. The mathematical methods that are important to interpretation are described and physical data are given in ten appendices covering 92 pages; special mention should be made of the table of molecular structure data established up to 1969.

The fundamental principles of all microwave transitions (nuclear magnetic resonances, electron spin resonances) are discussed; the application examples are concerned mainly with the rotational spectra of gaseous molecules. Instruments and measuring techniques are not described. The intention of the authors was to write a textbook *and* handbook for chemists, in which the theory is developed "from the simplest approach consistent with essential correctness and applicability". They have succeeded well in this aim. The printing and presentation are also outstanding.

Bernhard Schrader [NB 975 IE]

Elements of Chemical Kinetics. By *M. Prettre* and *B. Claudel*. Documents on Chemistry, Vol. 1. Gordon and Breach, Scientific Publishers, London 1970. 1st ed., xvi, 184 pp., bound, $ 18.—.

The purpose of this new series, "Documents on Chemistry", is to bring together the various aspects of chemistry that are often widely separated in more conventional presentations. Since it is intended to publish extensive original papers and specific seminars for advanced students in both French and English, the widest possible circle of readers should be reached. The first volume is concerned with elementary chemical kinetics and is mainly limited to reactions connected with the conversion of covalent bonds in simple molecules. In the first 93 pages concepts such as the rate and order of a reaction, activation energy, activated complexes, photochemical reactions, and chain reactions are explained by means of examples. The authors use a minimum of formal mathematics, but are also rather sparing with their illustrations. The second part contains descriptions of catalytic reactions, including acid-base catalysis, adsorption of molecules on solid surfaces, and the related contact catalysis, and there is even a very brief look at the *Michaelis-Menten* enzyme catalysis. Finally, the significance of kinetic problems in the optimization of syntheses under both laboratory and industrial conditions is discussed. At the end of each chapter there are simple numerical exercises and a few literature references, mostly of historical interest.

The book can be used as a first introduction to the problems and terminology of chemical kinetics, and is rather more detailed and less general than the corresponding sections in most of the physical chemistry textbooks. The few printing errors in the English edition are not a serious drawback. However, the phenomenological presentation and the selection of the material (and the price) are hardly likely to arouse any particular enthusiasm in chemistry students for this subject.

F. M. Pohl [NB 985 IE]

Carbenes, Nitrenes and Arynes. By *T. L. Gilchrist* and *C. W. Rees*. Thomas Nelson and Sons Ltd., London 1969. 1st ed., 131 pp., bound, $ 21.—.

A number of review articles and monographs have appeared in recent years on carbenes, nitrenes, and arynes. The present book is the first attempt to give a comprehensive picture of a field of research in which so much work has been done.

Chapter 1 indicates the relationships between carbenes, nitrenes, and arynes. Chapters 2—4 deal with the preparation and Chapters 5—8 with the reactions of these compounds. Finally, Chapter 9 shows their preparative applications.

In their introduction the authors express their intentions of taking the fullest possible account of recent work (the literature is covered up to 1968) and of providing a general survey rather than an exhaustive treatment. These intentions have certainly been realized, but they require a rigid selection of the individual reactions, so that many of them are given very brief treatment. This is particularly true of the Wolff rearrangement, described on p. 77. For example, the occurrence of ketocarbenes is stated to be improbable, and yet recent work suggests that they are found at any rate in photolytic reactions. Chapter 9 on the range of uses of carbenes, nitrenes, and arynes in syntheses could also be expanded a little. The book contains very few factual errors (pp. 11, 61, 62, 63, 106, and 108) and is practically free from printing errors.

The text is written in a very clear and understandable style. Most of the chapters contain references to the most important literature on the individual reactions. All in all, it is well worth the money, and can be recommended both to advanced students and to anyone who wants to become acquainted rapidly with the field concerned.

Heinz Dürr [NB 990 IE]

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Aromaticity and Pericyclic Reactions

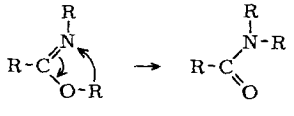
By Michael J. S. Dewar[*]

Pericyclic reactions formally resemble the conversion of one Kekulé structure into another; the transition state may be "aromatic", "nonaromatic", or "antiaromatic". Thermally induced pericyclic reactions proceed preferentially via aromatic transition states whereas their photochemical counterparts lead to products that are formed via antiaromatic transition states.

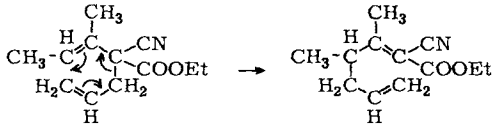
1. Introduction

For half a century organic chemists have recognized the possibility that certain reactions and molecular rearrangements might take place by a mechanism involving the concerted cyclic permutation of bonds round a ring of atoms. In the era of the classical electronic theory of *Lapworth* and *Robinson*[1] and *Ingold*[2], such mechanisms were proposed for a number of reactions using the current curved arrow symbolism to represent the displacement of electron pair bonds. The following are typical examples, involving rings of various sizes:

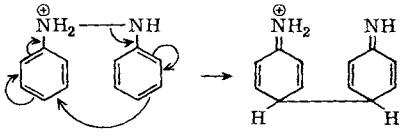
The isoamide-amide rearrangement[3]



The Cope rearrangement[4]



The benzidine rearrangement[5]



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However, although the possibility of such processes, which *Woodward* and *Hoffmann*[6] have termed *pericyclic*, was recognized at an early date, it is only in the last ten years that they have become a matter of major concern to organic chemists. There are three reasons for this.

First, reactions of this type present very difficult mechanistic problems, so much so that *Doering*[7] suggested the term "no mechanism reaction" for them. It is only recently that suitable experimental techniques (*e.g.* the analysis of secondary isotope effects) have been developed for their study.

Secondly, the earlier examples were rather featureless and limited in scope; the development of modern analytical techniques, in particular GLC and NMR spectroscopy, has suddenly opened up a field (*i.e.* nonionic thermal rearrangements) in which interesting pericyclic mechanisms abound.

Thirdly, under the stimulus of this new information, *Woodward* and *Hoffmann* formulated a set of rules[6] which systematized it in a very satisfactory manner.

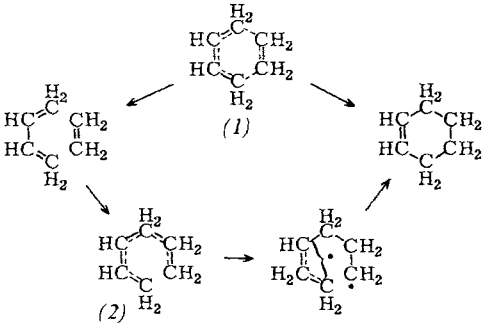
There can be no question concerning the value of the contribution by *Woodward* and *Hoffmann* in the formulation and application of these rules. Their work has brought order into a new and active field and has also led to the discovery of many interesting new reactions. Rules of this kind can of course be of value regardless of their origin; resonance theory provides a good example, the corresponding rules having been used successfully for many years by organic chemists with little understanding of their theoretical basis. On the other hand the analogy of resonance theory also shows the dangers inherent in this course; the literature is full of errors arising from the uninformed use of resonance theory.

Resonance theory also illustrates a third point; the success of a rule is no justification for the particular theoretical approach used to deduce it in the first place. Thus the original derivation of resonance theory by *Pauling* proved incorrect; a valid interpretation was given[8] only after the theory had been in general use for many years.

The purpose of this article is to review critically the various theoretical derivations that have been given for the Woodward-Hoffmann rules. It will appear that the best and simplest of these derives from an early treatment of pericyclic reactions which has for various reasons been largely overlooked.

2. Pericyclic Transition States as Aromatic Systems; Evans' Principle

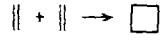
Thirty-five years ago the mechanism of the Diels-Alder reaction was still uncertain, the possibilities being a one-step process involving a cyclic transition state *(1)*, and a two-step process involving an intermediate biradical or zwitterion, produced *via* the linear transition state *(2)*.



During the reaction each carbon atom remains attached to three other atoms; it is reasonable to suppose that three of its valence AOs are used throughout to form localized σ bonds to them. The dotted lines in *(1)* and *(2)* then denote MOs formed by interaction of the six remaining carbon AOs, and containing all together six electrons.

The formation of multicenter MOs by mutual interaction of AOs depends on the latter overlapping in space but it does not depend on the geometry of overlap. In *(1)*, six AOs overlap in a ring, each AO with AOs of the two neighboring atoms; the situation is topologically equivalent to the overlapping of the six carbon 2p AOs in benzene to form cyclic π MOs. Likewise the overlap in *(2)* is topologically equivalent to that in 1,3,5-hexatriene. In other words, the delocalized electrons in *(1)* are topologically equivalent to, or isoconjugate with, the π MOs in benzene, and those in *(2)* to the MOs of hexatriene. The same factors that make benzene more stable than hexatriene, *i.e. aromatic*, should likewise make *(1)* more stable than *(2)*. On this basis we would therefore expect the one-step mechanism *via (1)* to be favored because the corresponding transition state is *aromatic*.

This argument was put forward by *M. G. Evans* in 1939[9, 10]. *Evans* and *Polanyi* had just published[11] their well known extension of the Eyring-Polanyi semiempirical method; *Evans* and *Warhurst*[9] set out to test this by applying it to the Diels-Alder reaction. In this treatment the transition state is first approximated as the crossing point of the potential curves for bond breaking and bond forming processes; the value so found for its energy is then corrected for resonance between the bond-broken and bond-formed structures. *Evans* and *Warhurst* pointed out the analogy noted above between the delocalized electrons in the transition state for the reaction between butadiene and ethylene and the π electrons of benzene and they accordingly calculated the resonance energy of this transition state by the same valence bond (VB) method that *Pauling* had used in his classical study of benzene. They estimated the resonance energy of the transition state to be 18 kcal/mole, about half *Pauling*'s value for benzene, and they estimated the overall activation energy for the reaction to be 18 kcal/mole, a value which was too low but of the right order. They also pointed out that the resonance energy for the transition state for the analogous dimerization of ethylene



should be small (because the valence bond method predicts cyclobutadiene to be nonaromatic); since the other terms in the expression for the activation energy seemed to be similar for both reactions, the activation energy of the Diels-Alder reaction should be less than that of ethylene dimerization by *ca.* 18 kcal/mole.

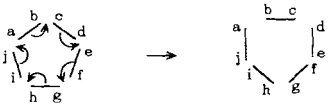
In the following year *Evans*[10] published a more detailed study of these reactions, using the Hückel MO method to calculate the resonance energies of the transition states. He also included calculations for the two-step reaction of butadiene with ethylene *via* the linear transition state *(2)*. He explicitly stated the analogy between the transition state *(1)* and benzene, and between the linear transition state *(2)* and 1,3,5-hexatriene, the resonance energies of *(1)* and of benzene being greater than those of *(2)* and hexatriene respectively.

There can therefore be no doubt that *Evans* fully recognized the role played by delocalization in the transition state of the Diels-Alder reaction and the analogy between the delocalized systems of the cyclic and linear transition states and the π systems of benzene and hexatriene respectively. He also recognized the difference between the Diels-Alder reaction with its six-membered transition state (analogous to benzene and so highly resonance stabilized) and the ethylene dimerization where the transition state should be stabilized to a much lesser degree, if at all. He also clearly stated that the additional resonance energy of the cyclic transition state *(1)* over the linear transition state *(2)* should be a factor in favoring the one-step reaction and he even gave quantitative estimates of the various resonance energies by the admittedly somewhat primitive theoretical methods then available.

This account of *Evans*' work seems necessary in view of recent attempts to belittle it and also because it seems to have been overlooked elsewhere, possibly because it was published just before the outbreak of World War II[12]. It is quite clear from his papers that he fully recognized the special features controlling the course of pericyclic reactions

and the basic ideas used to interpret π cycloaddition reactions can be applied equally well to other pericyclic processes.

A pericyclic reaction by definition involves a cyclic interchange of bonds around a ring of atoms, *e.g.*



Such a process is formally analogous to the conversion of one Kekulé structure for a cyclic polyene into the other. The transition state for the pericyclic reaction is therefore precisely analogous to the hybrid of classical structures in an intermediate "aromatic" structure for the polyene. If the polyene is aromatic, the intermediate structure is more stable than either classical structure and the reaction can proceed smoothly; if the polyene is antiaromatic, the conversion of one classical structure into the other involves an unfavorable intermediate. We can therefore relate the facility of a pericyclic reaction to the stability of the cyclic transition state relative to an open chain analog; by analogy with cyclic polyenes, we can then describe the cyclic transition state as being aromatic, nonaromatic, or antiaromatic, according to whether it is more stable than, as stable as, or less stable than the open chain analog. This obvious generalization of *Evans*' work leads to a simple rule for predicting the facility of pericyclic processes, a rule which should clearly be named for him and has accordingly been termed[13] *Evans' Principle*:

Thermal pericyclic reactions take place preferentially via aromatic transition states.

The problem of pericyclic reactions is thus identical in principle with that of aromaticity; any theory of aromaticity is *ipso facto* a theory of pericyclic reactions. The utility of this approach from the point of view of the practicing organic chemist then depends on the facility with which he can predict whether or not a given pericyclic transition state is aromatic.

In 1939 there was no satisfactory theory of aromaticity; indeed, no one had clearly recognized the possibility that cyclic conjugated systems might be antiaromatic, *i.e.* less stable than open chain analogs. Such a theory, and indeed the term "antiaromatic", was proposed in 1952[14] on the basis of a simple extension of the Hückel MO method, using perturbation theory. As we shall see presently, this treatment, which is a clear sequel to *Evans*' 1939 paper[10], provides a complete and simple account of pericyclic reactions of all kinds.

The paper by *Evans* and *Warhurst*[9] has had a similar sequel. *Mulder* and *Oosterhof*[15] have recently used an analogous valence bond treatment to explain the course of electrocyclic ring opening reactions and this approach could also be extended to other pericyclic processes. While it is satisfactory that their elegant treatment leads to conclusions similar to those given by the MO method, it suffers from several disadvantages by comparison. First, the MO method has proved generally superior to the VB method for the interpretation of organic chemistry. Secondly, as a result of this, few chemists now are familiar with the VB method. Thirdly, the procedure used by *Mulder* and *Oosterhof* can be applied only to simple monocyclic systems and so is less general than the MO approach.

3. The Frontier Orbital Method

A third approach that has been used to estimate the energies of pericyclic transition states is based on the Frontier Orbital (FO) method of *Fukui*[16]. In this the transition state for a bimolecular reaction is regarded as a perturbation of the reactants, the corresponding activation energy being given by second order perturbation theory. Since the only terms that survive[14, 17] are those involving interactions between a filled orbital of one component and an empty orbital of the other, and since the magnitude of the interaction between two orbitals varies inversely as the difference in energy between them, the main contributions arise from interactions between the highest occupied MO (HOMO) or *frontier* orbital of one component and the lowest unoccupied MO (LUMO) of the other. *Fukui* assumes that these terms dominate the situation so that all others can be neglected.

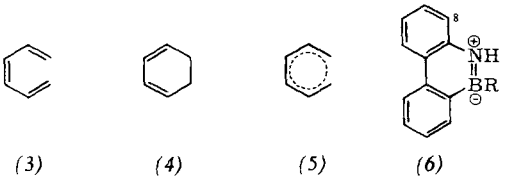
The original discussion[18] of electrocyclic reactions by *Woodward* and *Hoffmann* was formulated in terms of the FO method and *Fukui*[19] has recently extended it to the whole range of pericyclic processes. While superficially attractive, this approach suffers from several obvious limitations.

First, in order to use the FO method one needs to know the shapes of frontier orbitals. In simple cases these are determined by symmetry but in general they have to be calculated by procedures requiring the use of digital computers. Moreover, the form of the orbitals is not invariant to the procedure used to calculate them; the MOs given by different methods, or with different parameters, can vary very significantly.

Secondly, the FO method cannot in general be applied to unimolecular pericyclic processes because in this case first order perturbations are involved and these are of comparable magnitude for all the MOs. Consider, for example, the cyclization of 1,3,5-hexatriene *(3)* to 1,3-cyclohexadiene *(4) via* the pericyclic transition state *(5)*. The change in energy (δE_μ) of the MO ψ_μ on passing from *(3)* to *(5)* is given[14, 17] to a first approximation by

$$\delta E_\mu = a_{\mu 1} a_{\mu 6} \beta_{16}$$

where $a_{\mu 1}$ and $a_{\mu 6}$ are the coefficients in ψ_μ of the AOs of the terminal carbon atoms in *(3)* and β_{16} is the 1,6 resonance integral in *(5)*. The total difference in energy between *(3)* and *(5)* is a sum of the contributions δE_μ. There



(3) *(4)* *(5)* *(6)*

is no reason why that of the HOMO should dominate and in general it will not; the total energy difference is in fact given[14, 17] approximately by $2p_{16}\beta_{16}$ where p_{16} is the 1,6 bond order in *(3)*.

Thirdly, the FO method often leads to incorrect predictions, particularly in the case of molecules containing heteroatoms. A good example is provided[20] by derivatives of 10-bora-9-azaphenanthrene *(6)* which undergo electrophilic substitution most readily at the 8-position. All the MO treatments we have tried predict this position to lie almost on a node of the frontier orbital, the frontier orbital density being less there than at any other position in the molecule.

Fukui[19] avoids the first difficulty by confining attention to simple hydrocarbons where the general form of the HOMOs and LUMOs is determined by symmetry. The second difficulty is circumvented by the rather cavalier procedure of dissecting the π electron system into two parts so that the usual bimolecular procedure can be applied; thus the conversion of *(3)* to *(4)* is regarded as an internal Diels-Alder reaction between ethylene and butadiene moieties. Having established that the Woodward-Hoffmann rules hold for these special cases, it is then assumed that they will hold generally.

This kind of approach is of course useful as a guide in the search for generalizations; indeed, *Woodward* and *Hoffmann*[18] were originally so guided by a FO study of simple pericyclic reactions. However, such an argument is necessarily limited to the specific area where it is applicable, in this case to reactions of simple hydrocarbons. Consequently the use of the Woodward-Hoffmann rules in other connections has no real support from the FO method.

4. Conservation of State and Orbital Symmetry

An entirely different and very ingenious approach was suggested by *Longuet-Higgins* and *Abrahamson*[21], based on certain well known properties of molecular wave functions. If a molecule has some element of symmetry, the molecular wave function must conform[17] to that symmetry; thus in the case of a two-fold symmetry, *e.g.* a plane or center of symmetry, the wave function must be either symmetric, or antisymmetric, with respect to that symmetry operation. Any change in such a system which takes place with retention of symmetry must leave the symmetry of the wave function unchanged; if the wave function is initially symmetric, it must remain symmetric, and if initially antisymmetric, it must remain antisymmetric. Thus if the reactants in a reaction have a plane of symmetry, and if that symmetry is retained throughout the reaction, then the wave function must remain throughout either symmetric or antisymmetric.

One can on this basis correlate the states of the reactants with those of the products, plotting the energy of each state against a suitable reaction coordinate. If then the ground state of the reactants correlates with an excited state of the product, one can be sure that the reaction will be extremely unfavorable energetically because it will be impossible for the products to be formed in their ground state.

If the ground state of the reactants correlates with an excited state of the products, then of course the ground state of the products must correlate with an excited state of the reactants. The two lines on the correlation diagram (Figure 1) must cross. Such a crossing is normally forbidden; it occurs here only because the states have different symmetries. Any deviation from perfect symmetry will lead to a mixing of states in the crossover zone so that now the ground states of reactants and products correlate. This situation is indicated in Figure 1 for increasing loss of symmetry by the dotted lines a—c. It is, however, clear that the correlation plot will still tend to show a maximum which one would intuitively expect to be greater than for an analogous process in a system where symmetry is retained but where the ground states correlate with each other. In systems which are almost symmetric, the same qualitative distinction between "allowed" and "forbidden" reactions should therefore still hold as in cases where symmetry is rigorously maintained.

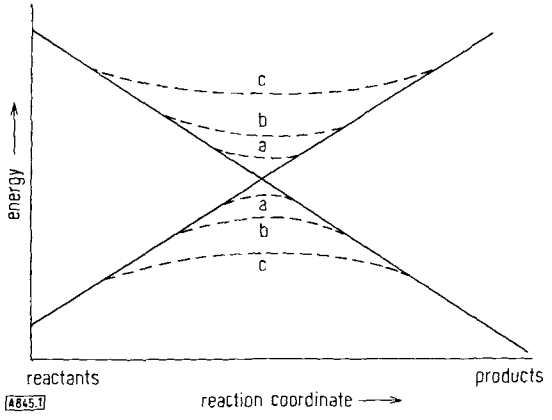


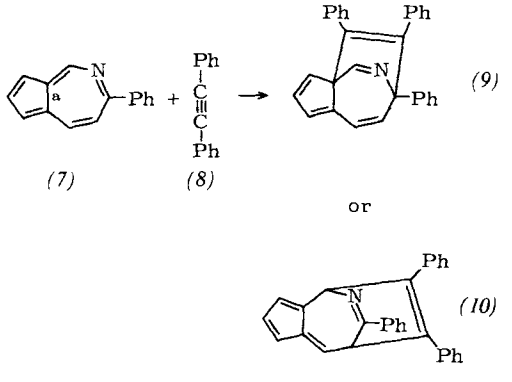
Fig. 1. Plot of energies of states *vs.* reaction coordinate for a process where symmetry is retained (—) and the effect (- - - -; a, b, c) of progressively removing the symmetry.

In the orbital approximation, the symmetry restrictions that apply to the total wave function also hold for the individual orbitals[17]. Individual MOs of the reactants can thus be correlated with MOs of the products and one can deduce the symmetry of the overall wave function of a given state from the symmetries of the MOs occupied in it. *Longuet-Higgins* and *Abrahamson*[21] applied this treatment to several simple pericyclic reactions of symmetrical molecules, assuming symmetry to be retained throughout, and showed that the reactions were "allowed" or "forbidden" in accordance with the predictions of the Woodward-Hoffmann rules.

A simpler version of this treatment has been adopted[6] by *Woodward* and *Hoffmann* as their preferred procedure for explaining pericyclic processes. Consider a reaction in which some element of symmetry is retained. Since the energies of the MOs must change continuously throughout, we can correlate MOs of the reactants with MOs of the products. The correlations can be represented on a diagram similar to Figure 1. In the ground states of the reactants and products, certain MOs are filled and the rest empty. If the filled MOs of reactants and products correlate with one

another, it is clear that the ground states must likewise correlate; the reaction is then "allowed". If, however, a filled MO of the reactants correlates with an empty MO of the product, and if the corresponding correlation of an empty MO of the reactants with a filled MO of the products (cf. Figure 1) involves a MO of different symmetry to the first, then the ground state of the reactants correlates with an excited state of the products and the reaction is consequently "forbidden". In this way one can base the distinction between "allowed" and "forbidden" reactions on correlations of orbital symmetry rather than of symmetry of states.

This approach is clearly superior to the FO method because it does apply quite rigorously to systems where symmetry is retained. The FO method is based on the assumption that one term in the expression for the second order perturbation dominates, an assumption which may be true in practice but for which there is no rigorous theoretical basis. However, both treatments suffer from the same basic defect of being inapplicable to systems where symmetry is not present. It is true that the present argument should also hold for systems where symmetry is "almost retained", but what do we mean by "almost"? Even small disturbances of symmetry can have far-reaching effects. Thus the strong absorption band of benzene at 208 nm ($\varepsilon \approx 10^4$) is due to a transition that would be forbidden were it not for small disturbances of the molecule from D_{6h} symmetry by molecular vibrations. Besides, we have to consider reactions where there is no semblance of symmetry involved, a good example being the π-cycloaddition reactions[22] of *(7)* and *(8)* to form *(9)* or *(10)* (see Section 6.2).



A further difficulty is the apparent disregard of symmetry shown by pericyclic reactions. If their course were controlled by conservation, or near conservation, of symmetry, the control should certainly become progressively less effective as the symmetry of the system is progressively destroyed. The experimental evidence[6] shows no indication of this. The Woodward-Hoffmann rules hold just as rigorously in systems totally lacking in symmetry as they do in symmetric ones. The rules are much more powerful—and much more useful—than they would be if this were not the case.

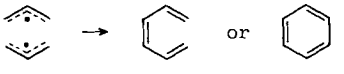
Although therefore this approach, like the FO one, has been of historical importance in leading to the original formulation of the Woodward-Hoffmann rules, it cannot be regarded as a satisfactory basis for them.

5. The PMO Theory of Aromaticity

In order to make use of Evans' Principle, one must have some simple procedure for telling whether or not a given system is aromatic; such a procedure was first developed in 1952[14].

The majority of chemical problems involve differences in energy between closely related structures; *Coulson* and *Longuet-Higgins*[23] first pointed out that these should logically be found by using perturbation theory and they were thus able to account for a number of phenomena in a simple way. However such differences in energy usually involve second order perturbations which cannot be estimated without a detailed knowledge of the MOs of the unperturbed species; these in turn can be found only by massive calculations. The breakthrough came with the discovery[14] of subterfuges by which first order perturbation theory could be used instead, under conditions where the first order perturbations can be estimated very simply; this led to a general "pencil and paper" theory of organic chemistry[17] which included a simple general theory of aromaticity.

The treatment[13, 14, 17] of aromaticity involves two steps. First one compares the energy of a given conjugated system with that of an isoconjugate hydrocarbon, *i.e.* one with the same number of π electrons and with all the heteroatoms replaced by carbon; one finds that the rules for aromaticity are the same for both. In the second, one compares the energy of the cyclic conjugated hydrocarbon with that of an open chain analog by relating both systems to open chain radicals or ions; thus benzene can be related to hexatriene by constructing both molecules by "union" of a pair of allyl radicals.



The unpaired electrons in such radicals occupy nonbonding MOs (NBMOs) that all have the same energy. The change in energy during union is consequently dominated by the first order perturbation involving the NBMOs. Moreover, the NBMO in such a radical can be found extremely simply by a method due to *Longuet-Higgins*[24] which involves a trivial calculation using pencil and paper; one can therefore predict very easily whether a given cyclic conjugated hydrocarbon will be more or less stable than the open chain analog, *i.e.* aromatic or nonaromatic. This approach is of course quite independent of symmetry and it can moreover be extended to individual rings in polycyclic systems; it therefore provides exactly the basis needed for the effective use of Evans' Principle.

In the case of a normal conjugated molecule, the π MOs are written as linear combinations of p AOs of the atoms. The two lobes of a p AO have opposite signs but the choice of absolute signs or *phases* is quite arbitrary. The resulting MOs are independent of this choice. For convenience one usually tries to choose the phases so that wherever two AOs overlap, they overlap in phase, *i.e.* positive with positive or negative with negative. In a normal conjugated

molecule one can of course satisfy this condition throughout (Figure 2a).

In 1959 *Craig*[25] pointed out that if one of the p AOs in a conjugated ring is replaced by a d AO, this condition can no longer be met; there will be a *phase dislocation* at some point in the ring (Figure 2b). Another example was pointed out by *Heilbronner*[26] in 1964; if we take a conjugated chain, twist it through 180°, and then join up the ends into a ring, the resulting π system will have a phase dislocation (Figure 2c). Here the π MOS, instead of forming rings above and below the nodal plane, form a continuous ring with the topology of a Möbius strip.

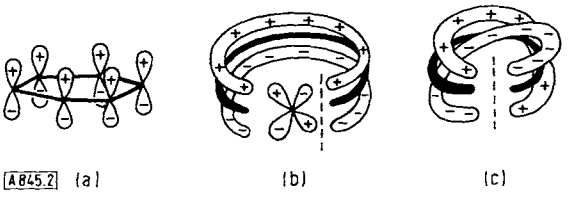


Fig. 2. (a) Normal Hückel conjugated system; (b), (c) phase dislocations (- - -) in antiHückel systems.

There are therefore two topologically distinct types of conjugated systems, normal *Hückel systems* in which the AOs can be chosen so that they all overlap in phase, and *antiHückel systems* where there will always be at least one phase dislocation, no matter how the phases of the AOs are chosen. There are only two possibilities in the case of a given ring because the number of phase dislocations can be increased or decreased two at a time by changing the phases of individual AOs; thus a ring is of Hückel type if the number of phase dislocations in it is even, of anti-Hückel type if the number is odd.

The PMO method can be applied equally well to anti-Hückel systems; in this way one can arrive at a set of general rules for aromaticity[13, 17], *viz.*:

a) Replace all heteroatoms by carbon atoms with an equivalent number of p (π) electrons; thus the nitrogen atom in pyridine (which contributes one p or π electron) is replaced by neutral C while the nitrogen atom in pyrrole, or the oxygen atom in furan (each of which contributes two p or π electrons) is replaced by $:C^-$.

b) Delete all essential single and double bonds, *i.e.* bonds that are respectively single or double in all possible classical (unexcited resonance) structures for the molecule. A good example is the central bond in azulene, whose π system is consequently equivalent to that of [10]annulene.

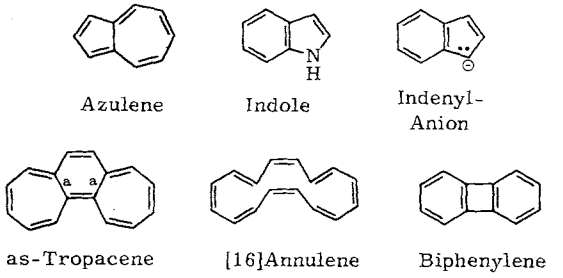
c) The aromaticity of each remaining ring is indicated in Table 1.

Table 1. Rules for aromaticity. + denotes aromatic character, − antiaromatic.

Type of conjugated system	Even-numbered rings [a]		Odd-numbered rings [b]			
	$4n$ atoms	$(4n+2)$ atoms	$(4n+1)$ atoms cations	$(4n+1)$ atoms anions	$(4n+3)$ atoms cations	$(4n+3)$ atoms anions
Hückel	−	+	−	+	+	−
antiHückel	+	−	+	−	−	+

[a] Neutral rings only.
[b] Radicals are nonaromatic (*i.e.* have predicted resonance energies similar to those of open-chain analogs).

It should be emphasized that the distinction between Hückel and antiHückel systems is a very profound one, depending on the phase relationships between the basis set AOs and quite independent of the MOs constructed from them. A topological distinction of this kind is obviously much more fundamental than one based on considerations of symmetry or molecular geometry. It should be noted that the signs attached to AOs here refer to the basis set AOs, not to MOs constructed from them; since an apparently similar notation has often been used (*e.g.* by *Woodward* and *Hoffmann*[6]) to indicate the symmetries of MOs, it is important that the two usages should not be confused.



Some examples of the rules for aromaticity follow:

Indole is isoconjugate with the indenyl anion; both rings are aromatic, Hückel-type systems, one ring being neutral with $(4n+2)$ atoms and the other an anion with $(4n+1)$ atoms.

Deletion of essential single bonds in as-tropacene leaves an antiaromatic [16]annulene ring having 16, *i.e.* $4n$ atoms (see Section 6.2).

In biphenylene, the central ring is antiaromatic ($4n$ atoms) and the terminal rings aromatic [$(4n+2)$ atoms].

6. The Use of Evans' Principle

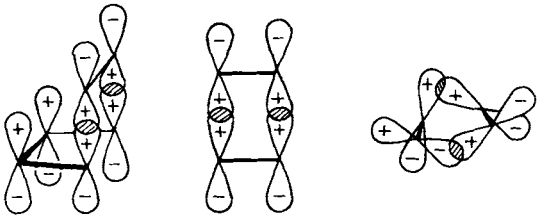
6.1. Introduction

Evans' Principle, together with the PMO treatment of aromaticity and the concept of antiHückel systems, provides in effect a simple theory of pericyclic reactions[13]. This could be regarded either as providing a satisfactory theoretical basis for the Woodward-Hoffmann rules or as a satisfactory alternative to them. The latter possibility will now be illustrated by a brief survey of pericyclic reactions in such terms.

6.2. Cycloaddition Reactions

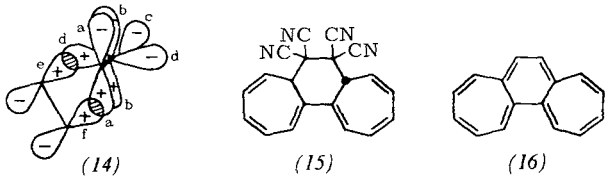
The Diels-Alder reaction has already been considered; it is easily seen from examination of the AOs involved [see *(11)*] that their phases can be chosen so that they all overlap in phase. The transition state is therefore of Hückel type and so isoconjugate with normal Hückel benzene, as *Evans* first pointed out[7]. The Diels-Alder reaction is, as predicted, a one-step pericyclic process[27]. On the other hand an analogous concerted combination of two olefins

to a cyclobutane, by *cis-cis* addition, would involve a transition state *(12)* isoconjugate with Hückel cyclobutadiene which is antiaromatic; here a two-step process *via* a biradical should be favored, as indeed appears to be the case[28]. A concerted addition of two olefins should, however, be possible if one of them undergoes *trans* addition, a feasible process if the reaction involves strained cyclic olefins where the double bond is twisted[29]; the corresponding transition state *(13)* involves a phase dislocation and so is isoconjugate with antiHückel cyclobutadiene which is aromatic. Such an addition has been observed in the dimerization of a *trans* cycloolefin[30] and the resulting dimer had the predicted *cis-trans* geometry.



(11) *(12)* *(13)*

Another interesting concerted reaction involving formation of four-membered rings occurs with ketenes[31]. This can be explained in terms of a transition state *(14)* in which the p AOs of the approaching olefin overlap with p AOs of the methylene and central carbon atom of the ketene, belonging to different π systems. In the transition state, the symmetry of the ketene is lost; the oxygen p AOs can then couple the π systems together. This is indicated in *(14)*, where a p AO (c) of oxygen (at the back) is represented as overlapping with both p AOs (b and d) of the central carbon atom. There is now an unbroken chain of overlap along the AOs a, b, c, d, and a and d overlap with the AOs (e and f) of the olefin. The resulting transition state is then isoconjugate with that in the Diels-Alder reaction. On this basis one would expect allene to show similar concerted 1,2 cycloadditions with suitable dienophiles, allene playing the role of the diene in a Diels-Alder reaction; reactions of this type are known but it has not yet been established that any of them involve concerted cycloaddition.

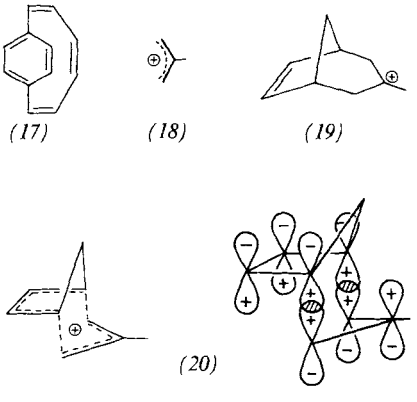


(14) *(15)* *(16)*

If the phases of the AOs are chosen so as to avoid phase dislocations inside each of the reacting molecules, *cis* addition takes place at lobes with the same phase and *trans* addition at lobes with opposite phase. The transition states for *cis-cis* or *trans-trans* addition are therefore of Hückel type, since the phases of the AOs can be chosen to avoid any phase dislocation, while the *cis-trans* addition involves an antiHückel transition state. It should be obvious that all the other cycloaddition reactions cited by *Woodward* and *Hoffmann*[6] can be explained immediately in these terms. Thus the transition state for the cycloaddition of tetracyanoethylene to heptafulvalene to form[32] *(15)* is isoconjugate with the tricyclic system *(16)*; since the transannular bonds here are essential single bonds, this is effectively the [16]annulene which is aromatic only in the antiHückel series. The reaction should therefore involve *cis-trans* addition; examination of models shows that it must be the heptafulvalene that adds *trans*, as indeed is the case[32], the adduct having, as predicted, the geometry indicated in *(15)*.

The π cycloaddition[22] of *(7)* to *(8)* noted above can be explained at once in these terms. The bond marked a in *(7)* remains an essential single bond throughout; disregarding it, the transition states for formation of *(9)* or *(10)* are seen to be isoconjugate with *(17)* which contains two fused aromatic rings (one with six, one with ten atoms). Note that the fact that *(17)* would be highly strained is irrelevant; any strain in such a system is due entirely to distortions of σ bonds and is irrelevant to the question of its aromaticity. Bonds of pπ:pπ type show no directional properties since p AOs are axially symmetric.

Similar arguments can obviously be applied to cycloadditions isoconjugate with ions. Thus the cycloaddition[33] of 2-methylallyl cation *(18)* to cyclopentadiene to form *(19)* involves a transition state *(20)* which is isoconjugate with the (aromatic) tropylium ion, while the numerous dipolar additions reported by *Huisgen et al.*[34] involve additions to olefins of compounds isoconjugate with allyl anion (*e.g.* $C_6H_5-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$) and so have transition states isoconjugate with the aromatic cyclopentadienate anion.



(17) *(18)* *(19)*

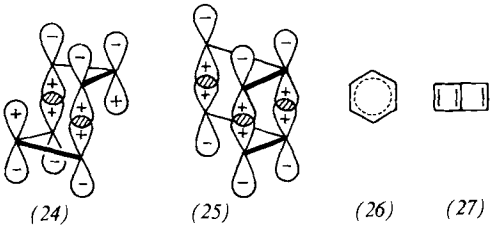
(20)

6.3. Claisen, Cope, *etc.* Rearrangements

The Cope rearrangement of a biallyl *(21)* to the isomer *(23)* is a concerted pericyclic process involving the transition state *(22)*. As *Doering* and *Roth* pointed out[35], this can exist in two distinct configurations *(24)* and *(25)* analogous to the "chair" and "boat" forms of cyclohexane. As indicated in *(24)* and *(25)*, the orbital overlap in them is equivalent to the π overlap in benzene *(26)* and bicyclohexatriene *(27)* respectively. Since the latter contains two antiaromatic cyclobutadiene rings, it is clearly less aromatic than *(26)*; we can therefore predict that the reaction should take place *via* the "chair" transition state *(24)*, as indeed it does[35].

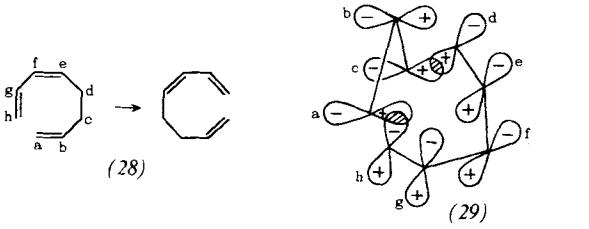


(21) (22) (23)

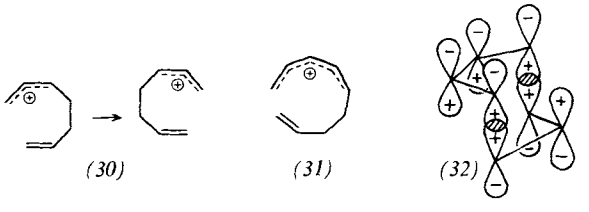


(24) (25) (26) (27)

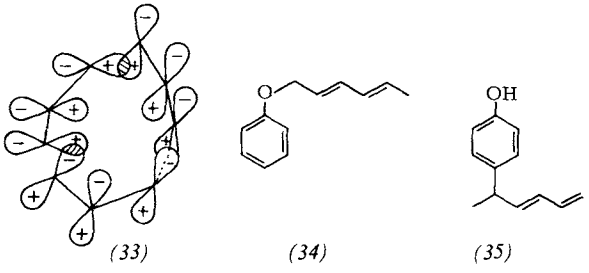
Exactly similar considerations should apply to other analogous rearrangements of structures isoconjugate with biallyl, *e.g.* the Claisen rearrangement which also[36] takes place *via* a "chair" transition state. One can obviously also envisage analogous rearrangements involving larger even-numbered rings and ions. In the case of $(4n+2)$-membered rings, the rearrangements should take place *via cis* transition states analogous to *(24)*. In the case of $4n$ membered rings, *e.g. (28)*, the rearrangement should occur only if the transition state has one phase dislocation; this is possible if the rearrangement involves a *trans* combination of the ends of the conjugated system [cf. *(29)*]. In rearrangements of ions the same principles apply; in the case of ions which are aromatic in the Hückel series, the rearrangements should be *cis*, in the case of those that are aromatic in the antiHückel series, *trans*. Possible examples might be the rearrangements of *(30)* and *(31)*, the former taking place *via* the *cis* transition state *(32)*, the latter *via* the *trans* one *(33)*.



(28) (29)



(30) (31) (32)

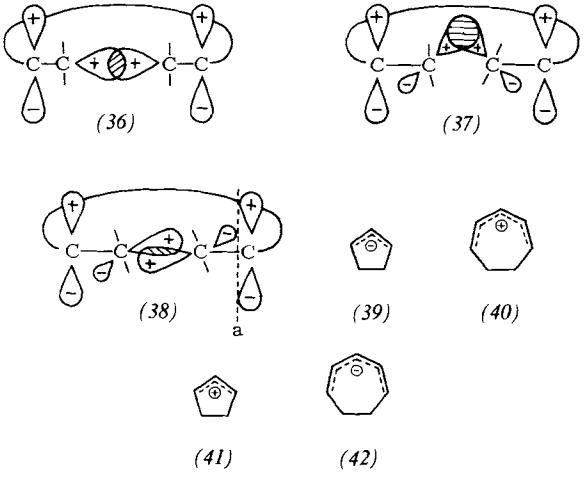


(33) (34) (35)

An interesting point is raised by the rearrangement of *(34)* to *(35)*, recently reported by *Fráter* and *Schmid*[37]. Here the transition state is again isoconjugate with *(17)*.

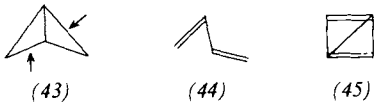
6.4. Electrocyclic Reactions[6]

The thermal conversion of cyclobutenes into butadienes, and of 1,3,5-hexatrienes into cyclohexadienes, are stereospecific processes which were among the first pericyclic reactions studied by *Woodward* and *Hoffmann*[6]. These processes are represented schematically below, *(36)* being the ring closed product and *(37)* and *(38)* the transition states involving reactions of respectively disrotatory[6] and conrotatory[6] stereochemistry. It is immediately obvious, as *Zimmerman*[38] has pointed out, that the disrotatory transition state *(37)* involves no phase dislocations and so is of Hückel type, whereas the conrotatory one involves a single phase dislocation [a in *(38)*] and so is of antiHückel type. Which of the two will be favored can be deduced at once from Table 1. Thus if the reaction involves rupture or formation of an even-numbered ring, the disrotatory path should be favored if the ring contains $(4n+2)$ atoms (as in cyclohexadiene) but conrotatory if it contains $4n$ (as in cyclobutene). In the case of odd-numbered ions, the disrotatory path should be favored in anions with $(4n+1)$ atoms [*e.g. (39)*] or cations with $(4n+3)$ atoms [*e.g. (40)*] and the conrotatory path in cations with $(4n+1)$ atoms [*e.g. (41)*] or anions with $(4n+3)$ [*e.g. (42)*]. These predictions of course agree with those of *Woodward* and *Hoffmann*[6] and have been confirmed for neutral rings with four or six atoms[6], for cations with three[39] or five[40], and for anions with five[41].



(36) (37) (38) (39) (40) (41) (42)

The present approach can also be applied to polycyclic systems. A good example is provided by bicyclobutane *(43)* which undergoes a thermal ring opening, by breaking of the bonds indicated by arrows, to butadiene *(44)*. The transition state is isoconjugate with bicyclobutadiene *(45)*; since the transannular bond is an essential single bond, this is equivalent to cyclobutadiene and so antiaromatic in the Hückel series. The transition state must therefore involve just *one* phase dislocation, so one of the bonds in



(43) (44) (45)

(43) must undergo disrotatory rupture, the other conrotatory, a prediction in agreement with experiment[42].

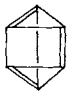
Other examples are provided by the benzene isomers, benzvalene *(46)* and prismane *(47)*. Although the conversion of either into benzene involves a huge decrease in energy[43,44], derivatives of them are surprisingly stable[44]. This can be understood at once in terms of the present treatment. Thus the conversion of *(46)* to benzene involves the same type of bond rupture as does the conversion of *(43)* to *(44)*. However the ethylene bridge in *(46)* makes it imperative that both bonds undergo disrotatory fission, or both conrotatory fission; steric considerations make it impossible for one to break by a disrotatory, the other by conrotatory, process. The conversion of *(46)* to benzene therefore involves an antiaromatic transition state. A similar situation arises in the case of prismane where the transition state for direct conversion to benzene is isoconjugate with the bridged benzene analog *(48)*; this, like the analogous boat transition state for the Cope rearrangement (see Section 6.3), is antiaromatic.



(46)



(47)

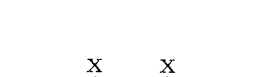


(48)

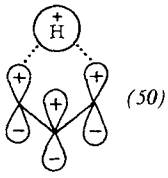
One might add that much of the current theorizing concerning possible types of pericyclic reaction seems to have ignored one of the fundamental principles of reaction theory. In a reaction where one bond is broken and another formed, activation is usually necessary since the new bond does not begin to form until the old one has been severely weakened. A reaction involving rupture of two bonds will require correspondingly more activation and one involving rupture of three bonds more again. For this reason the majority of organic reactions involve rupture and/or formation of just one bond and hardly any involve rupture of three. Reactions involving rupture of two or more bonds normally occur only if they are strongly exothermic and if the transition state is also highly resonance-stabilized (*i.e.* aromatic). It has, of course, been known for many years, from the theory of potential surfaces of *Evans*, *Polanyi*, and *Bell*[17,45], that the more exothermic a reaction, the smaller in general its activation energy (cf. [46]); however, exothermicity alone is not sufficient to enable a reaction involving multiple bond fission to take place under normal conditions. The conversion of *(47)* to benzene may well be a stepwise process.

6.5. Sigmatropic Rearrangements

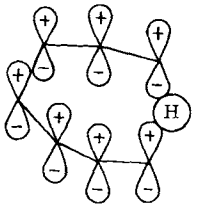
This term was introduced by *Woodward* and *Hoffmann*[6] to describe rearrangements of the type symbolized in *(49)*. A classic example is the migration of allylic hydrogen to an adjacent conjugated chain of atoms. If the hydrogen atom remains on the same side of the plane of conjugated atoms (*suprafacial* rearrangement[6]), it is obvious that the transition state will be of Hückel type [cf. *(50)*]. Such reactions should occur only if the transition state contains a $(4n+2)$-membered ring, *i.e.* by 1,5 or 1,9 migration, not 1,3 or 1,7. This is now well known to be the case[47]. Conversely, an antarafacial[6] rearrangement, in which hydrogen migrates to the other side of the nodal plane of the π system, involves a transition state of antiHückel type [see *(51)*]; this geometry should be favored in 1,3, 1,7, *etc.*, rearrangements.



(49)

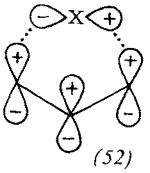


(50)

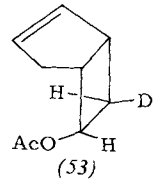


(51)

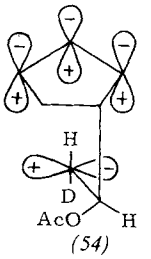
In cases where the migrating group uses a p AO for bonding, the rules for antarafacial and suprafacial reactions can be inverted. Thus the transition state *(52)* for 1,3 migration is clearly of antiHückel type and so aromatic. Intramolecular allylic migrations of halogen have been known for some time and probably involve this mechanism; the classic example, however, is that of *Berson* and *Nelson*[48]. Thermal rearrangement of *(53)* gives *(55)*, *via* the transition state *(54)*.



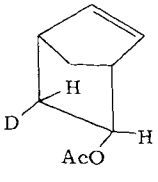
(52)



(53)



(54)

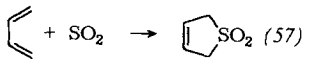


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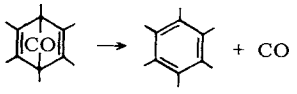
6.6. Chelotropic Reactions

Chelotropic is the appropriate term devised by *Woodward* and *Hoffmann*[6] to describe reactions in which an odd-numbered ring is formed by insertion of an atom between the ends of a linear polyene, or the converse regeneration of the polyene from the cyclic adduct. The formation of sulfone *(57)* from butadiene and sulfur dioxide, and the pyrolysis of Diels-Alder adducts *(58)* to carbon monoxide and benzene derivatives are good examples. *Woodward* and *Hoffmann*[6] also include in this category cycloadditions to simple olefins, *e.g.* the addition of carbenes to olefins to form cyclopropanes; for reasons indicated below it seems

better to classify reactions of this type separately, chelotropic processes being taken to involve reactions in which polyenes are involved (see Section 6.7).

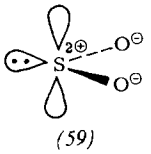


(56) (57)

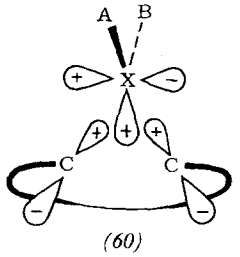


(58)

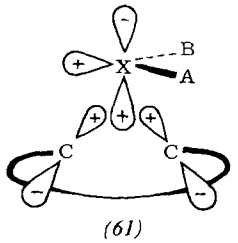
Since the reagent forms two new bonds in the reaction, it must have two free AOs. These moreover must contain just two electrons in order that the reaction take place with no net transfer of charge. Typically, the reagent has, or can be written as having, a filled hybrid AO and an empty p AO, the hybrid AO being filled since hybrid AOs are lower in energy. Thus one can write such a structure *(59)* for SO_2.



(59)



(60)



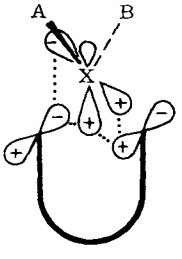
(61)

The terminal methylene groups of the polyene undergo rotations out of coplanarity during the reaction, analogous to those undergone by the terminal methylene groups in an electrocyclic process; chelotropic reactions can therefore be subdivided into disrotatory and conrotatory types. In the transition state, the two AOs of the reagent interact with the p AOs of the terminal methylenes to form two cyclic conjugated systems each with an odd number of atoms. That involving the filled hybrid AO will have one more electron than there are atoms in the ring and so will be isoconjugate with an odd cyclic hydrocarbon anion while that involving the empty p AO of the reagent will likewise be isoconjugate with an odd hydrocarbon cation.

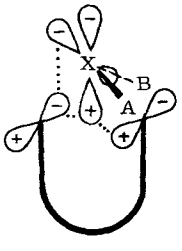
In a disrotatory process, the best overlap between the AOs of the reagent and the terminal p AOs of the olefin should occur in the geometry indicated in *(60)* where the reagent approaches in a direction perpendicular to the polyene. the hybrid AO undergoing σ-type overlap, and the p AO π-type overlap, with the terminal p AOs. This approach will be superior to one in which the role of the AOs is inverted [see *(61)*] for two reasons. First, the σ-type overlap in *(61)* is inferior since half the p AO is wasted; secondly the π overlap is also inferior since only the p component of the hybrid AO can take part.

The σ-type overlap leads to a Hückel cyclic system, the π-type overlap to an antiHückel one [see *(60)*]. If the polyene contains $4n$ atoms, the Hückel type system is isoconjugate with a Hückel $(4n+1)$-membered cyclic hydrocarbon anion and so is aromatic, while the antiHückel system is isoconjugate with an antiHückel $(4n-1)$, *i.e.* $(4n'+3)$-membered cyclic hydrocarbon cation and so is also aromatic. The transition state for such a process is thus doubly aromatic, while that for reaction of a polyene containing $(4n+2)$ atoms will be doubly antiaromatic. This type of addition should therefore be favored in the case of polyenes with $4n$ atoms, *e.g.* butadiene; the formation of butadiene sulfone, and related processes, are disrotatory[6]. It is easily seen that the rules are inverted for the other mode of approach *(61)*; here the transition state is aromatic for polyenes with $(4n+2)$ atoms and antiaromatic for those with $4n$. Disrotatory addition is therefore always possible though more favorable in the case of $4n$-membered polyenes.

In a conrotatory process, it is equally clear that the best mode of addition of the reagent will be in the plane of the polyene as indicated in *(62)*. Again, the best overlap will be attained if the reagent approaches so that its hybrid AO overlaps in σ-type fashion, and its p AO in π-type fashion, with the terminal p AOs of the olefin *(62)*. In this case, however, the cyclic conjugated system arising from the σ-type overlap is of antiHückel type, that from π-type overlap of Hückel type; the transition state will therefore be aromatic if the polyene contains $(4n+2)$ atoms and antiaromatic if it contains $4n$. Again, one can envisage an alternative less favorable mode of approach *(63)* [cf. *(61)*] in which the roles of the hybrid and p AOs of the reagent are interchanged and where the transition state is now aromatic if the polyene contains $4n$ atoms and antiaromatic with $(4n+2)$.



(62)



(63)

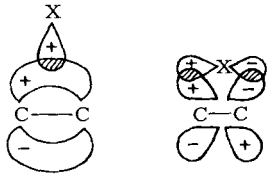
Either mode of approach is therefore possible with polyenes of either type [$4n$ or $(4n+2)$ atoms]; since the disrotatory and conrotatory transition states involve different types of overlap, it is impossible to predict on the basis of any qualitative theory whether one of them may be favored to the extent that one of the less satisfactory modes of reaction [*(61)* or *(63)*] may on balance prove superior to the more satisfactory mode [*(60)* or *(62)*] of opposite type. The experimental evidence suggests that the two most favorable modes of reaction are in fact *(60)* and *(62)*,

polyenes with $4n$ atoms reacting by the disrotatory path[6] and those with $(4n+2)$ atoms by the conrotatory one[49].

Woodward and *Hoffmann*[6] did not consider the geometry of approach indicated in *(60)* and *(61)*; however their arguments can be extended in an obvious manner to this case.

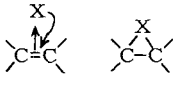
6.7. π-Complex Reactions

It has long been recognized[50] that olefins can behave as Lewis bases, forming *π complexes* with acceptors by donation of their π electrons *(64)*; the majority of electrophilic reactions of olefins involve processes of this kind[17, 50, 51]. In cases where the acceptor has a filled p, π, or d orbital, the π complex can be further stabilized by back-coordination *(65)* into the empty antibonding π MO of the olefin; as the present author first pointed out[50], the structure of olefin-transition metal complexes can be explained in such terms. In a complex of this type, there is in effect a double bond between the olefin and the acceptor; the resulting structure can be represented either in terms of two opposed dative bonds *(66)* or in terms of a three-membered ring *(67)*, the two descriptions being equivalent[50].



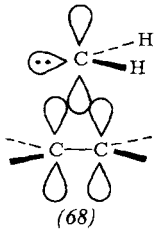
(64)

(65)



(66)

(67)

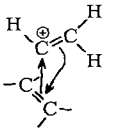


(68)

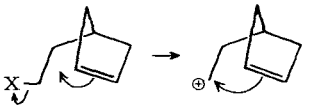
Reagents of suitable type should therefore be able to add to olefins to form products containing three-membered rings, a process which bears obvious analogies to the chelotropic reactions discussed above and has been classified accordingly by *Woodward* and *Hoffmann*[6]. However, the back-coordination of the reagent to the olefin in such a reaction is a side issue; it serves only to facilitate the primary acid-base interaction of the olefin behaving as a Lewis base with the reagent acting as a Lewis acid. The resulting π complexes occur as intermediates in many reactions where the reagent is incapable of back-coordination[51]; many of these moreover are molecular rearrangements quite unrelated to chelotropic processes.

Reactions of this type leading to three-membered rings include the epoxidation of olefins by formal addition of oxygen atoms and the addition of singlet carbenes to olefins to form cyclopropanes. In the case of carbene addition the stereochemistry of approach must of course be that indicated in *(68)*, as *Skell*[52] has remarked, in order that the empty p AO of the carbene should overlap with the filled bonding π MO of the olefin. In this case back-coordination involves a pseudo-π interaction of the filled hybrid AO of the carbene with the empty antibonding π MO of the olefin [cf. *(61)* and *(63)*].

A further reaction falling into this category is the addition of vinyl cations to olefins to form cyclobutyl or cyclopropylmethyl derivatives. The π complex *(69)* formed by addition is identical with the "non-classical" carbonium ion or π complex that appears[51] to be an intermediate in the solvolysis of certain cyclobutyl or cyclopropylmethyl esters.



(69)



(70) *(71)*

Woodward and *Hoffmann*[6] classify this process as a $[{}_2\pi_s + {}_2\pi_a]$ cycloaddition; however, there is no reason to suppose that it does not involve a simple one-center attack on the carbonium ion by the olefin analogous to the corresponding reactions of alkyl cations, *e.g.* the formation[51] of norbornyl cation by the π route *(70)* → *(71)*.

6.8. Photochemical Pericyclic Processes

A number of pericyclic reactions take place photochemically, usually with consequences different from those of analogous thermal reactions[6]. Light must therefore play some role other than that of merely providing energy to overcome an activation barrier. Moreover the reactions almost certainly involve a direct conversion of the excited reactants into products in their ground state because the conversion of excited reactants into excited products is in many cases energetically impossible[53]. Such processes must involve a breakdown in the Born-Oppenheimer approximation, the product being formed in a vibronically excited form of its ground state.

At some point in the reaction, the molecule must therefore pass from an electronically excited, vibronically unexcited configuration to one than is electronically unexcited but vibronically excited. It is well established that processes of this kind occur more easily, the smaller the degree of vibronic excitation involved; places where the potential surfaces for the excited and ground states approach one another therefore act as weak points in the former where the photochemically excited reactant can leak through to the ground state.

As *Dougherty*[54] has pointed out, one can on this basis derive an extension of Evans' Principle to cover photochemical pericyclic reactions. According to the PMO theory, there is a close connection[55] between the excitation energies of conjugated systems and their aromaticity. The relative stabilities of analogous aromatic, nonaromatic, and antiaromatic alternant[17] hydrocarbons are determined mainly by the energies of the highest occupied MOs. The electrons in these are more tightly bound in aromatic

systems, and less tightly in antiaromatic systems, than in nonaromatic ones (Figure 3); from the pairing theorem[17], the energies of the lowest unoccupied MOs vary in a mirror image manner (Figure 3). The first excitation energies of aromatic compounds should therefore be greater, and those of antiaromatic compounds less, than those of analogous nonaromatic compounds; this certainly appears to be the case. Thus the first absorption band of naphthalene is at much shorter wavelengths than that of a corresponding open chain polyene while the reverse is true for heptalene whose absorption extends into the infrared[56].

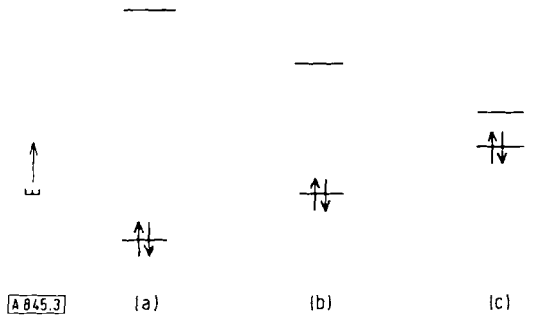


Fig. 3. Highest occupied and lowest unoccupied MOs of analogous aromatic (a), nonaromatic (b), and antiaromatic (c) hydrocarbons.

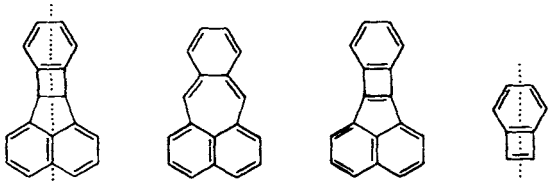
In the case of a pericyclic reaction, the potential surfaces for the ground state and the first excited state should therefore come particularly close together for geometries corresponding to antiaromatic transition states of thermal reactions. These should therefore be the regions where the Born-Oppenheimer approximation should be most prone to fail and where deexcitation of the photoexcited system should consequently be most probable. The photochemical reaction should therefore tend to lead to the conversion of the reactants into the antiaromatic transition states that correspond to "forbidden" thermal pericyclic reactions and so lead to the corresponding products. This argument provides an extension of Evans' Principle to such processes:

Photochemical pericyclic reactions lead preferentially to the products that would be formed thermally via antiaromatic transition states.

In other words the rules for photochemical pericyclic reactions should be exactly opposite to those for corresponding thermal ones, a generalization that was proposed[13] on the basis of a less rigorous PMO argument by the present author and which forms a logical extension of the original MO approach by *Evans*[10]. The same conclusion has also been reached by *van der Lugt* and *Oosterhof*[53] on the basis of a valence bond treatment that represents an analogous extension of the original study by *Evans* and *Warhurst*[9].

The experimental evidence seems to be entirely consistent with this generalization[6]. Thus the *cis-cis* dimerization of olefins to cyclobutanes takes place very readily under the influence of light while the Diels-Alder reaction remains unaffected; likewise the stereochemistry of electrocyclic and chelotropic processes is inverted in the case of photochemical reactions.

One recent apparent exception[57] to this generalization serves in fact as further support for it. The photochemical conversion of *(72)* to *(73)* does not involve the lowest excited state. The reason for this is that the chromophores in *(72)* are uncoupled and the first absorption band corresponds to excitation of the naphthalene moiety; such excitation should be ineffective for converting *(72)* into *(73)*. The transition state for this process is isoconjugate with *(74)* in which the naphthalene and cyclobutabenzene moieties are isolated from one another by essential single bonds. For photoinduced disrotatory ring opening to occur, the excitation energy must be located in the benzene. Excitation of the naphthalene moiety could then lead to reaction only if the excitation energy could be transferred to the nascent cyclobutabenzene system. However both *(72)* and cyclobutabenzene *(75)* have planes of symmetry (···); their wave functions must be symmetric or antisymmetric for reflection in those planes. Since the lowest excited state of *(72)* is, like the ground state, symmetric while that of *(74)* is antisymmetric, transfer of energy from the naphthalene to the nascent benzocyclobutadiene system in *(72)* is forbidden.



(72) *(73)* *(74)* *(75)*

6.9. Catalysis by Transition Metals

A number of cases are now known where pericyclic reactions are catalyzed by transition metals. Some of these involve direct chemical reaction of the metal with the reagent to form organometallic species that undergo further conversions[58]; such processes, while interesting and important, are unrelated to normal pericyclic processes. There is, however, reason to believe that in certain cases transition metals can influence the course of pericyclic reactions solely by coordinating with unsaturated or aromatic systems in the reactants; such a process would be an example of true metal catalysis of a pericyclic reaction.

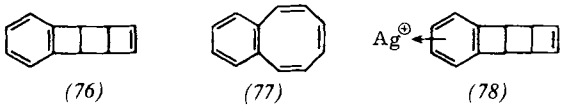
The π complex theory[50] of metal-olefin complexes attributes their stability to back-coordination of d electrons of the metal into an antibonding π MO of the olefin; this argument suggests that antiaromatic hydrocarbons should form particularly strong metal complexes since they have a pair of electrons in an MO of very high energy (Figure 3), very suitable for donation to the metal, and at the same time an empty MO of very low energy (Figure 3), ideal for back-coordination. Cyclobutadiene does indeed form exceptionally stable complexes of this type[59], while cyclooctatetraene can apparently form analogous ones with metals containing electrons in AOs of the correct symmetry (*i.e.* f) for back-coordination (uranocene[60]).

The analogy between the delocalized electrons of pericyclic transition states and the π MOs of aromatic and antiaromatic conjugated molecules leads one to suppose

that antiaromatic transition states should likewise form very stable complexes to transition metals of suitable type, *i.e.* ones towards the end of each transition series where d electrons are available for back-coordination. If then the the reactants are aromatic, or non-aromatic, coordination to such a transition metal should facilitate a reaction involving an antiaromatic transition state; for the coordination energy of the metal to the latter should be greater than to the reactants. It is of course impossible to predict on the basis of qualitative arguments such as this whether or not such catalysis will be sufficient to overcome the inherent barrier to reaction due to the antiaromaticity of the transition state; one can, however, predict with some confidence that if catalysis by transition metals of pericyclic reactions is observed, it will be confined to processes which are normally "forbidden" because the transition states are antiaromatic. One could state this conclusion in the form of a second amendment to Evans' rule:

Transition metals may catalyze pericyclic reactions if, and only if, they involve antiaromatic transition states.

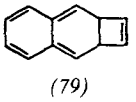
A probable example of such catalysis is that observed by *Pettit* and his collaborators[61]. The codimer *(76)* of cyclobutadiene and cyclobutabenzene is thermally quite stable because opening of either cyclobutene ring, to form ultimately benzocyclooctatetraene *(77)*, would involve an antiaromatic transition state (disrotatory ring opening of a cyclobutene ring, conrotatory opening being stereochemically impossible). Conversion of *(76)* to *(77)* does take place on heating but requires 3 hours at 150 °C to go to completion. If, however, a silver salt is added to a solution of *(76)* at room temperature, the conversion is complete in less than 10 seconds. Silver is known to form very strong complexes with benzene rings; in the complex *(78)* opening of the cyclobutene ring adjacent to benzene is catalyzed by coordination of Ag^+ to the latter. The product *(79)* undergoes further reaction to *(77)* very readily; for here the starting material is nonaromatic whereas the transition state for disrotatory ring opening is isoconjugate with cyclobuta[*b*]naphthalene *(80)* which is on balance aromatic, containing two aromatic rings and one antiaromatic one. A further nice touch is that treatment of *(76)* with platinum salts leads[61] to an equally facile conversion into *(81)*. Platinum coordinates much more strongly to olefins than to benzene rings so the catalytically active species is presumably *(82)*; here platinum catalyzes disrotatory ring opening to *(81)* which is now stable



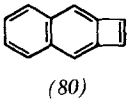
(76)

(77)

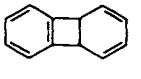
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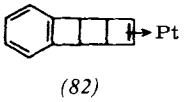
(79)



(80)



(81)



(82)

because, unlike *(79)*, it contains an aromatic ring. The transition state for disrotatory ring opening of *(81)* will again be isoconjugate with *(80)* and so contain on balance one aromatic ring; conversion of *(81)* into this transition state is therefore much less favorable than conversion of *(79)* into the corresponding one because *(79)*, unlike *(81)*, is nonaromatic.

7. Results of Recent MO Calculations

The treatments of pericyclic reactions in terms of the FO method, of conservation of symmetry of states, or of Evans' Principle, are all essentially qualitative; while one can consequently predict from them that conrotatory opening of cyclobutene should be favored, one cannot give any numerical estimate of the difference in activation energy, and so of rate, between the conrotatory and disrotatory paths. *Woodward* and *Hoffmann*[6] have expressed the belief that the factors opposing "forbidden" pericyclic reactions are so great that no exceptions to the Woodward-Hoffmann rules are possible; they consider that apparent exceptions, such as the thermal conversion of *(76)* into *(77)*, must take place by non-concerted mechanisms. On the other hand *Evans* and *Warhurst*[9] using an admittedly very crude VB treatment, estimated the difference in activation energy between the Diels-Alder reaction of butadiene with ethylene, and the corresponding "forbidden" dimerization of ethylene to cyclobutane, to be 18 kcal/mole, a difference that could easily be countered by steric effects. Thus the relief of ring strain in the initial conversion of *(76)* into *(79)* or *(81)* must be greater than 50 kcal/mole, amply adequate to permit the observation of "forbidden" disrotatory ring opening if the difference between the "allowed" and "forbidden" paths is of the order of 20 kcal/mole.

The parallel between the delocalized MOs of pericyclic transition states and the π MOs of cyclic conjugated molecules suggests that the differences between aromatic and antiaromatic systems should be comparable for both. In the case of conjugated hydrocarbons, techniques have been developed[62–64], based on the Hückel σ, π approximation and the use of semiempirical SCF MO methods for the π electrons, that enable their heats of atomization, and hence their resonance energies[62,63], to be estimated with high precision. The resonance energy of benzene on this basis is[62,63] *ca.* +20 kcal/mole, that of cyclobutadiene, assuming a symmetrical square geometry, −34 kcal/mole[65], and the corresponding resonance energies of both the aromatic and the antiaromatic series decrease with increasing ring size. The difference in resonance energy between the aromatic and antiaromatic series is therefore *ca.* 50 kcal/mole for small rings and decreases with ring size. The difference is furthermore reduced by bond alternation; the most stable form of cyclobutadiene, with a rectangular geometry, is predicted[65] to have a resonance energy of −18 kcal/mole. Since the overlap of AOs in pericyclic transition states is likely to be less than in π systems, and since bond alternation can occur very easily in antiaromatic transition states, one would expect the effects embodied in the Woodward-Hoffmann rules, and described by Evans'

Principle, to produce a maximum variation in activation energies of *ca.* 30 kcal/mole.

In order to proceed further, one must include all the valence electrons in one's calculation so that one can estimate directly the effect of delocalization in transition states. One must also be able to calculate the properties of molecules, in particular their heats of atomization and geometries, with "chemical" accuracy. Recently a semiempirical SCF MO procedure (MINDO/2[66, 67]) has been developed which comes close to meeting these requirements and calculations have been carried out for several pericyclic reactions with results that seem relevant to the present discussion.

First, the difference in activation energy between the disrotatory and conrotatory paths for several simple electrocyclic reactions, *i.e.* the ring opening of cyclopropyl radical, anion, and cation to corresponding allyl derivatives, was found to be *ca.* 30 kcal/mole, in agreement with the estimate above[68].

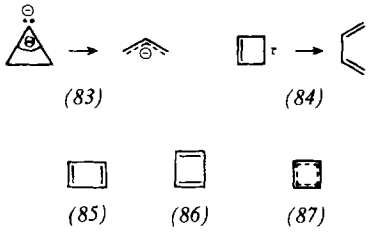
Secondly, the difference in activation energy between the two paths for the Cope rearrangement, *via* the "chair" *(24)* and "boat" *(25)* transition states, was correctly predicted[67, 69] and it was shown that the "boat" transition state is disfavored because of the antibonding interaction indicated in *(25)* and *(27)*. In confirmation, the calculated activation energies for a number of Cope rearrangements, in particular those of bullvalene, barbaralane, and semibullvalene, reproduced closely the observed variation in rates[70].

Thirdly, a remarkable and unexpected feature was encountered in carrying out calculations for the electrocyclic ring opening of cyclopropyl to allyl, or cyclobutene to butadiene[68].

In a "normal" reaction, one can represent the reaction path as a plot of energy *versus* a reaction coordinate, the latter being any dimension in the system (*e.g.* a bond length or bond angle) that varies monotonically during the reaction. This can be done if there is a single valley leading from the reactants to the products; if one then minimizes the energy with respect to all other variables for each value of the reaction coordinate, one arrives at a series of points at the bottom of the valley separating reactants from products. The plot of energy *versus* the reaction coordinate is then a section across the potential surface, along the bottom of the valley in question.

When, however, calculations were carried out for the "forbidden" electrocyclic ring opening of cyclobutene and cyclopropyl anion by disrotatory paths, or of cyclopropyl cation by a conrotatory one, using the apical angle θ [in *(83)*] or the bond length r [in *(84)*] as reaction coordinates, this standard technique failed. In each case there were two distinct minima in the potential surface for each value of θ or r. Further investigation showed that the potential surface is as indicated in Figure 4 which shows a two dimensional contour map of energy as a function of θ (or r) and ϕ, ϕ being the angle of twist of the methylene groups that undergo disrotatory or conrotatory rotation during the reaction. For any value of θ (or r) there are two stable geometries, one corresponding to the arrangement of bonds in the reactants and one to that in the products, while intermediate configurations have a higher energy.

As we have seen, a pericyclic reaction involves a cyclic permutation of bonds round a ring of atoms. The reaction



(83) *(84)*

(85) *(86)* *(87)*

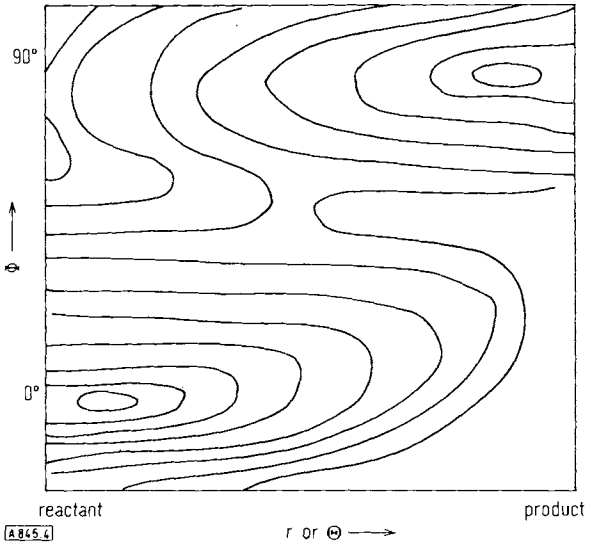


Fig. 4. Potential surface for "forbidden" electrocyclic reactions; ϕ is the angle of twist of the methylene groups from reactants ($\phi = 0$) to product ($\phi = 90°$).

can formally be regarded as the conversion of one Kekulé-like structure into another. In the transition state the system must have an intermediate geometry. If the transition state is aromatic, this intermediate structure has a lower energy than either of the "classical" structures corresponding to reactant or product; there will then be just *one* minimum in the potential surface for each value of a given reaction coordinate and consequently a single valley, leading from reactants to products, in the potential surface. This situation indeed held for the analogous "allowed" reactions, *e.g.* the conrotatory opening of cyclobutene.

If, however, the transition state is antiaromatic, the intermediate structure has a *higher* energy than either "classical" structure. The situation is analogous to that in cyclobutadiene where the classical structures *(85)* and *(86)* are more stable than the intermediate *(87)*. There are consequently *two* distinct valleys in the potential surface, corresponding to the reactant and product; the transition state is now the low point in the ridge separating the two valleys.

According to this argument, the same situation should arise in any reaction proceeding *via* an antiaromatic transition state; we have already found this to be the case for the "forbidden" *cis, cis* dimerization of ethylene to cyclobutane.

These calculations thus confirm in a rather dramatic and unexpected way the picture on which Evans' Principle is based. They also suggest that the energy factor favoring reactions with aromatic transition states are by no means overwhelming. On this basis the terms "allowed" and "forbidden" seem unfortunate in view of the connotations they carry from molecular spectroscopy. Resonance stabilization or destabilization of the transition state is only one of the factors affecting the rate of a pericyclic reaction and one that is by no means necessarily dominant. It would seem more appropriate to refer to the two types of pericyclic process as *aromatic* and *antiaromatic*, emphasizing that the antiaromatic reactions are no less possible than the existence of antiaromatic conjugated systems.

In this connection it should be pointed out that *Zimmerman*[38] and others have used the term Möbius system for those termed here antiaromatic. The term Möbius seems unsatisfactory for two reasons. First, the MOs of many antiaromatic transition states [*e.g. (38)*] do not have the topology of a Möbius strip; secondly, the topological distinction between aromatic and antiaromatic systems was first pointed out by *Craig*[25] on a different basis.

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Vanadium and Chromium Catalysts for Polymerization of Ethylene

By G. Henrici-Olivé and S. Olivé[*]

In the present progress report literature data concerning homogeneous catalyst systems based on vanadium and chromium are reviewed and complemented by a combined study of the magnetic properties and the polymerization activity of such systems. The results show that vanadium forms active species as V(III) and as V(II), but chromium only as Cr(II); models are suggested for the polymerization process.—A comparison with heterogeneous systems (Phillips catalyst) allows the establishment of some general principles concerning the activity of the catalyst and the properties of the polymers.

1. Introduction

The catalysts used for the industrial production of linear polyethylene are based essentially on either of two transition metals: titanium or chromium. Whereas the former is one of the components of the classical Ziegler systems[1], the latter represents the fundamental constituent of the Phillips catalyst[2]. Vanadium, situated between these two metals in the Periodic System, should be expected to have comparable catalytic activity. In fact there are numerous papers and patents referring to vanadium based catalyst systems for the polymerization of ethylene. However, none has reached commercial importance, perhaps due to the high molecular weights of the products. The specific use of vanadium-based systems appears to be for the copolymerization of ethylene and propylene[3,4]. Furthermore the name of vanadium will be coupled for ever with the first case of a stereospecific polymerization of an α-olefin with a homogeneous catalyst (syndiotactic polypropylene[5,6]).

The mechanism of the polymerization of ethylene on commercial, titanium based heterogeneous catalysts has lost a great part of its mystery as a consequence of a deeper knowledge obtained in the study of homogeneous systems[7,8]. It is now generally agreed that the active center is an alkylated titanium species with one vacant site in its coordination sphere, where the monomer can be coordinately bonded to the transition metal. The propagation step consists in the insertion of the olefin into the titanium-carbon bond [eq. (1)].

$$\begin{array}{l} H_2C{=}CH_2 \\ \quad\downarrow \\ (L_x)\text{-}Ti\text{-}R \longrightarrow (L_x)\text{-}Ti\text{-}CH_2\text{-}CH_2\text{-}R \end{array} \qquad (1)$$

The electron-donor-acceptor properties of the other ligands (L_x) of the titanium center have to be such that the Ti-carbon bond is stable in the absence of coordinated ethylene, and acquires just sufficient destabilization on coordination to permit the insertion reaction. It appears that Ti(IV), Ti(III), and Ti(II) are active valence states, each of them, however, having different requirements concerning the ligands L_x for suitable activity. (See recent reviews on the mechanistic aspects of the polymerization of ethylene with titanium based catalysts[9,10].)

How far has our knowledge advanced in the case of vanadium and chromium based catalysts? The valence states of V(IV), V(III), and V(II), as well as of Cr(V), Cr(III), and Cr(II) have been claimed for the active species *(vide infra)*. Although, after the experience gained with Ti, various valence states might be expected to be active, a look at the organometallic chemistry and the work carried out to synthesize and stabilize metal-carbon bonds of vanadium[11,12] and chromium[13,14] casts some doubt on the existence of alkyl groups or growing chains attached to V(IV), Cr(V), and to some extent (at $T > 0\,^{\circ}C$) also to Cr(III).

In the following a study of the present state of knowledge, concerning homogeneous as well as heterogeneous systems, will be supplemented by recent results obtained by the authors using homogeneous vanadium and chromium catalysts, with the aim of reaching some general conclusions concerning valence state, structure of the active species, and ligand requirements in the case of these two transition metals.

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2. Homogeneous Systems

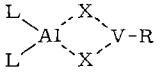
2.1. Present State

The first soluble vanadium catalyst for the polymerization of ethylene was reported in 1958 by *Carrick*[15]. Vanadium tetrachloride, aluminum bromide, and triphenyl- or triisobutylaluminum in cyclohexane constitute a system able to polymerize ethylene at 60 °C.

Extraction of the catalytic solution with sulfuric acid and polarographic analysis showed the vanadium to be exclusively divalent. The reduction of the original V(IV) was accomplished in less than one minute, but no further reduction to V(I) or V(0) was observed.

On the other hand, VCl_2 and VBr_2 are not soluble in cyclohexane, nor are they catalytically active. They can, however, be solubilized by complex formation with $AlBr_3$. Addition of an aluminum alkyl to these solutions then also provides an active catalyst.

From these facts *Carrick* concluded that the active species in the VCl_4 system is also a V(II)-Al complex, and in analogy to bridge-bonded Ti—Al complexes[16] structure *(1)* was suggested (L = alkyl or halogen, X = halogen, R = alkyl or growing chain).



(1)

The aluminum alkyl was later replaced by tetraphenyltin[17], and it was shown that the first process to occur in the system is the formation of an aluminum alkyl[17, 18]. *Van der Kerk et al.*[19] demonstrated that the combination of $AlBr_3$ and the organometallic compound $[(C_6H_5)_4Sn$ or $(C_6H_5)_3Al]$ could be replaced by $(C_2H_5)AlCl_2$, leading to a catalyst of comparable activity. The same authors[20] deduced from a spectroscopic investigation of the system VCl_4 (or $VOCl_3$) with $(C_2H_5)AlCl_2$ in cyclohexane at room temperature that the catalyst precursor is a V(II) species complexed to an aluminum alkyl. It is assumed that the active species forms only under the influence of trace amounts of oxygen (compare also *Carrick et al.*[21]), the valence state of the vanadium in the active species is said to be uncertain.

In 1962, *Bier et al.*[22] reported evidence for V(III) in the active species of the system $VOCl_3/(C_2H_5)_3Al_2Cl_3$ in heptane when used as catalyst for the copolymerization of ethylene with propylene (20 °C). They found a certain catalyst depletion with time, accompanied by a decrease of the concentration of V(III) in the solution. Both phenomena followed approximately the same rate law. The authors concluded that the active species consists of a V(III)-Al complex which is deactivated on reduction V(III) → V(II).

Natta et al.[23] also found V(III) to be the active valence in systems consisting of VCl_4 or $V(acac)_3$ (acac = 2,4-pentanedionate) with aluminum alkyls when used at −78 °C as catalyst for the syndiotactic polymerization of propene. The authors stated that a necessary condition for catalytic activity is the presence of at least one halogen ligand at either of the two components. The catalytic solutions are stable only at low temperature; on heating to room temperature inactive solid VCl_2 precipitates.

The system $V(acac)_3/(C_2H_5)_2AlCl$ shows the same catalytic behavior as the VCl_4 catalyst, thus eliminating V(IV) as the active valence. From the observation of constant polymerization rate (with the VCl_4 system), and the fact that only a small amount of the vanadium is active, it is deduced that the active species is continuously formed and destroyed to guarantee a steady state concentration. The catalyst is assumed to be VCl_2R complexed with the aluminum alkyl. The following mechanism is proposed for its formation and destruction:

$$VCl_4 \xrightarrow{R_2AlCl} VCl_2R_2$$
$$VCl_2R_2 \longrightarrow VCl_2R + R^*$$
$$VCl_2R + \text{monomer} \longrightarrow VCl_2P$$
$$VCl_2P \longrightarrow VCl_2 + P^*$$

P = polymer chain and P* = polymer radical

i.e. a dialkylated V(IV) species is proposed as the catalyst precursor.

Lehr et al.[24], however, discovered, with the same catalyst system and by ESR measurements (cf. Section 2.2), that after a few minutes at −78 °C practically all V(IV) is reduced, presumably to V(III), thus eliminating V(IV) species as possible catalyst precursor. A non-alkylated V(III) compound is suggested instead, which on alkylation becomes the catalyst. This opinion has been opposed recently by *Sváb*[25] who deduced, from an oxidimetric investigation of the systems VCl_4 (or $VOCl_2$) with several aluminum alkyls at varying temperatures, that at −78 °C the active species is $(C_2H_5)VCl_3$.

Thus there is agreement among different workers concerning certain points: the active species is a complex containing vanadium as well as aluminum; one of the catalyst components must contain at least one halogen ligand; no valence lower than V(II) is active. Disagreement has been found concerning the mechanism of the formation of the active species (pathways *via* dialkylated V(IV) and *via* non-alkylated V(III) species have been proposed), and concerning the valence state of the transition metal (V(IV), V(III), and V(II)).

On the other hand, homogeneous chromium based catalyst systems for the polymerization of ethylene have rarely been reported. A few literature references (including patents)[26–28] are not particularly clear about the physical state of the catalysts used. The only declaredly homogeneous system appears to be tris(π-allyl)chromium(III) as described by *Wilke et al.*[29] in a report on the conversion of ethylene at room temperature to high molecular weight polymer with an IR spectrum essentially coincident with that of Ziegler polyethylene, but with poor solubility, presumably due to crosslinking. Mechanism and valence state of the Cr in the active species have not been investigated.

2.2. Magnetic Measurements

An early ESR study with vanadium catalysts was carried out by *Natta et al.*[23] with the systems mentioned in the previous section (*e.g.* $VCl_4/(C_2H_5)_2AlCl$). Whereas the

active catalyst solution did not exhibit any ESR signal at $-78\,^{\circ}C$, the loss of activity on heating to room temperature was accompanied by the appearance of a broad one-line signal, identified as belonging to solid VCl_2.

Lehr[24] used ESR in an ingenious way to prove his hypothesis that VCl_4 is reduced immediately by $(C_2H_5)_2AlCl$ at $-78\,^{\circ}C$, and therefore could not be the precursor of the active species. V(IV) in solutions of VCl_4 is not detectable by ESR at temperatures above $9\,^{\circ}K$[30]. But VCl_4 can easily and quantitatively be converted into the VO^{2+} ion by quenching with ethanol. Since the vanadyl ion has a strong and well characterized ESR signal, the disappearance of V(IV) could easily be monitored. It was found that less than 0.07% of V(IV) remained after five minutes.

2.2.1. Choice of Suitable Systems

For a combined study of magnetic properties and polymerization activity we chose vanadyl bis(2,4-pentanedionate), $VO(acac)_2$, and chromium tris(2,4-pentanedionate), $Cr(acac)_3$, as transition metal components. Both are crystalline compounds which can be obtained in high purity. They are soluble in hydrocarbon solvents, stable enough in air for weighing operations, and quite stable under dry argon. Because of these properties the chosen compounds compare favorably with, *e.g.*, VCl_4 or $VOCl_3$, which are extremely air sensitive liquids, and with $VOCl_2$, which is insoluble in hydrocarbons and highly deliquescent.

Both $VO(acac)_2$ and $Cr(acac)_3$ form homogeneous catalyst solutions with $(C_2H_5)_2AlCl$. The stability of these solutions depends to some extent on the ratio of Al/M (M = transition metal). At low ratios, *i.e.* low Al content, the solutions tend to become turbid after some minutes, but this can be overcome by addition of phosphanes or phosphites. The measurements described below were therefore carried out in the presence of these stabilizing ligands.

2.2.2. Magnetic Measurements with Vanadium Systems

A recent ESR investigation[31] of the reaction of $VO(acac)_2$ with alkylaluminum chloride revealed that the acac ligands are replaced rapidly by chlorine. The evidence is as follows: $VO(acac)_2$ dissolved in toluene presents the typical eight-line signal of the free VO^{2+} ion (Fig. 1a). This signal does not change in the presence of triethyl phosphite. However, if ethylaluminum dichloride is added to a solution containing the phosphite, a new signal appears almost immediately (Fig. 1b). Each of the eight vanadium lines of the pure vanadyl spectrum is now split into a 1:2:1 triplet, indicating the interaction of the unpaired electron of the vanadium with two equivalent phosphorus nuclei.

The complex giving the signal in Fig. 1b can be decomposed by the addition of tetrahydrofuran. A vanadyl signal similar to that of Fig. 1a, but not identical, is then obtained. The spectra of $VO(acac)_2$ and $VOCl_2$ show a small but significant difference in the vanadium hyperfine splitting constant a_V (300 ± 2 and 287 ± 2 MHz, respectively), which allows the conclusion that the vanadyl center now bears chlorine ligands instead of the original acac ligands. The latter are assumed to be now bonded to aluminum which

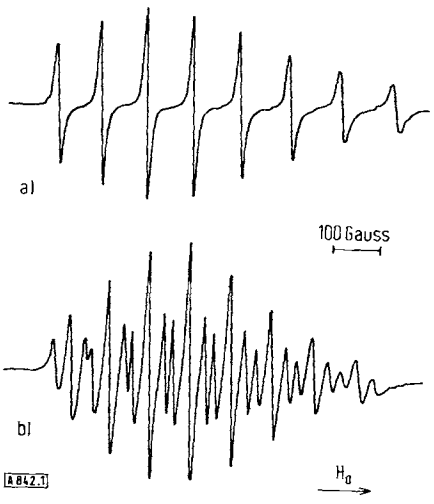
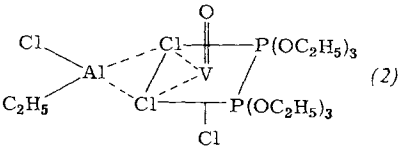


Fig. 1. ESR signals of vanadyl compounds in toluene. a) $VO(acac)_2$ alone, b) $VO(acac)_2/(C_2H_5O)_3P/(C_2H_5)AlCl_2$, V:P:Al = 1:6:10.

does not form part of the complex. The ligand exchange appears to be very rapid.

If the decomposition of the complex with THF is made a few minutes after the addition of the aluminum alkyl, essentially all vanadium is recovered as VO^{2+}, *i.e.* in this short time interval no reduction has taken place. On the other hand, $VOCl_2$ in the presence of triethylphosphite gives the triplet signal (Fig. 1b) only if aluminum alkyl is added[31]. Thus, in order to obtain the signal it is not sufficient only to replace the acac ligands by chlorine, but complex formation with the aluminum alkyl must also be possible. Presumably a bridge-bond is formed which completes an octahedral configuration as shown in *(2)*.



(2)

After longer time intervals the intensity of the signal in Fig. 1b decreases somewhat, indicating a slow reduction, presumably to V(III). With $(C_2H_5)_2AlCl$ instead of $C_2H_5AlCl_2$ the same ESR signal is observed, but the reduction rate is considerably higher. At a ratio of Al/V > 5 the V(IV) disappears so rapidly that no ESR signal can be detected, not even immediately after mixing of the components. With $(C_2H_5)_3Al$ the acac ligands also disappear, but the reduction goes through to V(0) which is stabilized as its bis-toluene complex, identified by the ESR signal reproduced in Fig. 2[32]. Each of the eight vanadium lines is split by the ten ring protons of two toluene molecules.

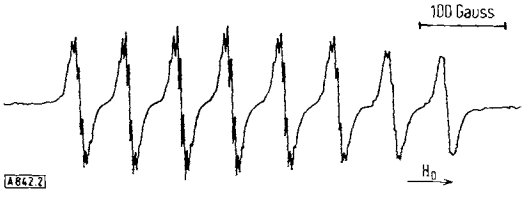


Fig. 2. ESR signal of bis-toluene-V(0) [32].

(This signal was erroneously attributed by *Shiulydin et al.*[33] to a complex containing one V(II) and two aluminum alkyls.)

The reduction reactions occurring in the V/Al catalyst systems are best investigated by magnetic susceptibility measurements. We determined the effective magnetic moment, μ_{eff}, of the vanadium in the system $VO(acac)_2/(C_2H_5)_2AlCl$ in benzene at different ratios of Al/V, in the presence and absence of stabilizing phosphanes and phosphites. From these data the average number of unpaired electrons per vanadium was calculated, making use of the spin-only formula, which is a good approximation for vanadium in its different valence states[34].

The results of the magnetic measurements are shown in Fig. 3. The data are obtained five minutes after mixing the components, the solutions then being completely homogeneous. At Al/V < 100, there is a tendency for the solution to become turbid after some 20—60 minutes, especially in the absence of stabilizing phosphorus compounds. At Al/V > 100 the solutions are stable and the magnetic data do not change with time.

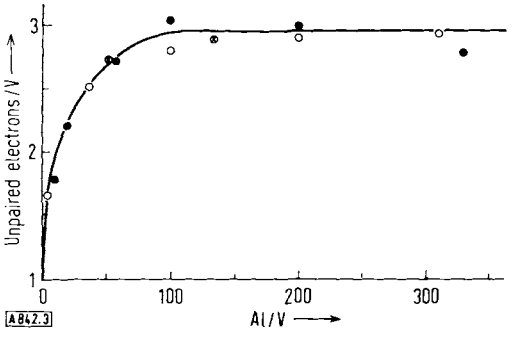


Fig. 3. Average number of unpaired electrons per vanadium center in the system $VO(acac)_2/(C_2H_5)_2AlCl$. ●: without stabilizer; ⊗: with $(C_6H_5)_3P$; ○: with $(C_2H_5O)_3P$. P/V = 6; $T = 20°C$.

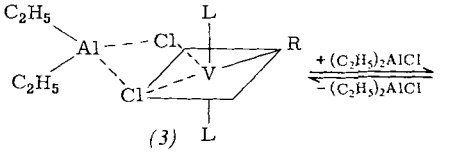
Fig. 3 shows a steady increase from one to three unpaired electrons per vanadium center in the range of Al/V from 0 to 100, the limiting values corresponding to V(IV) and V(II) respectively. At Al/V = 100 practically pure V(II) is reached. No further reduction takes place, not even at Al/V > 300. The presence of phosphorus compounds does not essentially affect the reduction process.

Table 1 gives the valence distribution at different ratios of Al/V. These numbers are computed from the data of Fig. 3. Since it has been proved by ESR that no V(IV) is detectable at Al/V > 5 immediately after mixing the components, the magnetic effect must be distributed between V(III) and V(II). The fraction of 6% of V(III) at Al/V ≥ 100 is probably not real, but is due to a small deviation of the true values of the molar susceptibility, χ_{mol}, from those calculated with the spin-only formula for V(II) and V(III) (6330×10^{-6} and 3370×10^{-6} e.m.u., respectively).

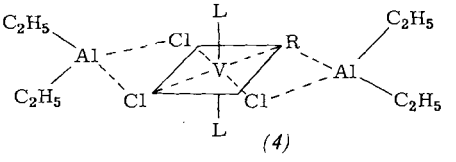
Table 1. Fractions of V(III) and V(II) after the reaction of $VO(acac)_2$ with $(C_2H_5)_2AlCl$. (Computed from the data of Fig. 3.)

Al/V	Unpaired electrons	$\chi_{mol} \times 10^6$ (e.m.u)	V(III) (%)	V(II) (%)
20	2.3	4110	75	25
50	2.7	5360	33	67
100	2.95	6150	6	94
300	2.95	6150	6	94

From the ESR experiments cited above we know that the acac ligands do not form part of the reduced vanadium complex. On the other hand it should be noted that with $(C_2H_5)_2AlCl$ it is not possible to obtain the bis-benzene-V(0) complex which is formed with $(C_2H_5)_3Al$. Presumably the presence of chlorine ligands at the vanadium center permits the formation of a bridge complex with one or two aluminum alkyl molecules which stabilizes the vanadium in the valence state V(II). Thus, the final stable V(II) complex may well be an equilibrium mixture of structures *(3)*



(3)



(4)

and *(4)* (R = ethyl or chlorine). The ligands L completing the octahedral structure might be solvent, phosphane, phosphite, or aluminum alkyl (cf. Section 2.3.2).

2.2.3. Magnetic Measurements with Chromium Systems

The chromium in $Cr(acac)_3$ is paramagnetic ($3d^3$). From the magnetic susceptibility of a benzene solution the magnetic moment $\mu_{eff} = 3.84$ BM can be obtained which, with the spin-only formula, corresponds to 2.96 unpaired electrons per chromium center.

The addition of $(C_2H_5)_2AlCl$ to the solution at ratios of Al/Cr < 200 results in the immediate appearance of turbidity and, after some minutes, the formation of a precipitate. In the presence of triethyl phosphite, however, the solution remains homogeneous. At ratios of Al/Cr ≥ 200, no precipitation is observed even in the absence of phosphite.

We measured the magnetic susceptibility of the homogeneous solutions at different ratios of Al/Cr, and calculated the average number of unpaired electrons per Cr center. These data are represented in Fig. 4.

In the range of Al/Cr from 0 to 20 the number of unpaired electrons decreases from three to about two. At higher ratios this number starts to increase; it again reaches a value of three at Al/Cr ≈ 70, and apparently tends asymptotically to four at Al/Cr > 400. The data given in Fig. 4 were recorded five minutes after mixing the components. There is still some variation with time which is shown in Table 2. In the absence of phosphite and at Al/Cr = 300 the final value of four unpaired electrons is almost reached after one hour (run 2). With $(C_2H_5)AlCl_2$ the process indicated by the change from two to four unpaired electrons appears to be slower than with $(C_2H_5)_2AlCl$ (run 3).

Our interpretation of the experimental findings given in Fig. 4 and Table 2 is as follows:

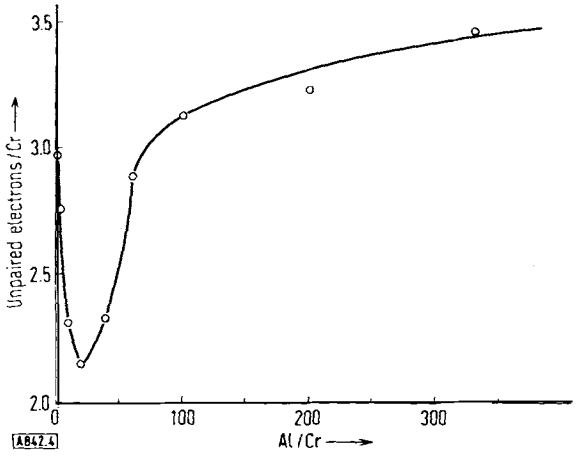


Fig. 4. Average number of unpaired electrons per chromium center in the system $Cr(acac)_3/(C_2H_5)_2AlCl/(C_2H_5O)_3P$; P/Cr = 6; T = 20 °C.

Table 2. Average number of unpaired electrons per chromium center as a function of time. $[Cr(acac)_3]_0 = 20 \times 10^{-3}$ mol/l, Al/Cr = 330, benzene, 20 °C.

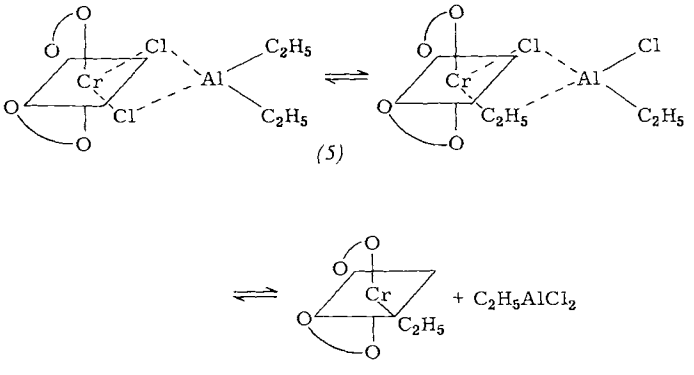
Run	Al-alkyl	$(C_2H_5O)_3P/Cr$	t (min)	Unpaired electrons per Cr
1	$(C_2H_5)_2AlCl$	6	5	3.42
			60	3.71
			120	3.73
2	$(C_2H_5)_2AlCl$	0	5	3.73
			60	3.88
			120	3.88
3	$(C_2H_5)AlCl_2$	0	5	2.89
			60	3.68
			120	3.72

Cr(II) ($3d^4$) complexes are, with very few exceptions, octahedral[35]. In this symmetry two arrangements are possible for the four 3d-electrons, depending on the energy differences between the t_{2g} orbitals (d_{xy}, d_{xz}, d_{yz}) and the e_g orbitals ($d_{x^2-y^2}$, d_{z^2})[34]. In a strong ligand field this separation, Δ, is large. In this case it is energetically more favorable that all four electrons stay in the lower lying t_{2g} orbitals, although pairing energy has to be expended. On the other hand, in a weak ligand field Δ is relatively small, and the promotion of one electron to the e_g level is favored. Consequently, Cr(II) is expected to have two unpaired electrons in a strong ligand field, and four in a weak field.

Thus the course of the curve in Fig. 4 represents the reduction Cr(III)→Cr(II) (low spin) in the region of Al/Cr ≤ 20. At higher ratios of Al/Cr we observe the transition from low spin to high spin configuration. A reasonable explanation for this behavior is a ligand exchange without variation of the symmetry of the complex. The acac ligands are known to be strong field ligands[36, 37]. We suggest that in the region of Al/Cr > 20 acac ligands are replaced by ligands producing a weaker field, presumably chlorine. In the case of vanadium this kind of exchange was demonstrated by ESR measurements (preceding section). However, in the case of $Cr(acac)_3$ too, a substitution of acac ligands by other ligands has already been observed on several occasions. *Hein*[38] reported the formation of phenylchromium compounds during the reaction of $Cr(acac)_3$ with phenylmagnesium bromide in ether. The reaction with triethylaluminum has also been described[39], including the formation of C—O—Al bonds and the evolution of ethane and ethylene. Presumably the alkylchromium compounds originating from the substitution of the acac ligands by ethyl groups are completely unstable in the absence of stabilizing ligands. If this latter reaction is carried out in aromatic solvents, zerovalent and low-valent chromium can be stabilized as bis-arene complexes, as evidenced by the ESR signal of bis-arene-Cr(I)[32].

Summarizing the magnetic measurements in the case of chromium, it can be said that the reaction of $Cr(acac)_3$ with aluminum alkyls leads to ligand exchange and reduction. If chlorine ligands are available, Cr(II) is stabilized, and no further reduction takes place even at very high ratios of Al/Cr. In the special case of $(C_2H_5)_2AlCl$ we propose the following reaction path:

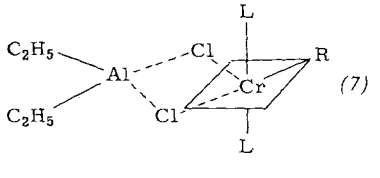
Exchange of the first acac with Cl leaves one coordination site free, where an aluminum bridge bond can establish [cf. titanium[8, 9] and vanadium (Section 2.2.2) systems].



If this bridge bond opens again, leaving an ethyl group at the metal center, the very unstable Cr(III)-carbon bond cleaves, resulting in a Cr(II) species *(6)* that is probably stabilized by phosphite ligands L (precipitation occurs in the absence of phosphite).

$$2(acac)_2Cr(III)C_2H_5 \longrightarrow \underset{(6)}{2(acac)_2Cr(II)L_2} + C_2H_4 + C_2H_6$$

Further exchange of the acac ligands for Cl or C_2H_5 may then lead to a species *(7)* similar to that formulated above



for the case of vanadium, perhaps also in equilibrium with a complex having two bridges.

2.3. Polymerization of Ethylene

2.3.1. Polymerization with Vanadium Systems

Fig. 5 shows the ethylene uptake in solutions of the $VO(acac)_2/(C_2H_5)_2AlCl$ catalyst at 20°C in the presence of a phosphane and at different ratios of Al/V. (For experimental methods see Reference [8].) At Al/V < 20, essentially no uptake is observed. The polymerization rate has a maximum at Al/V = 50, and then decreases steadily to Al/V = 500.

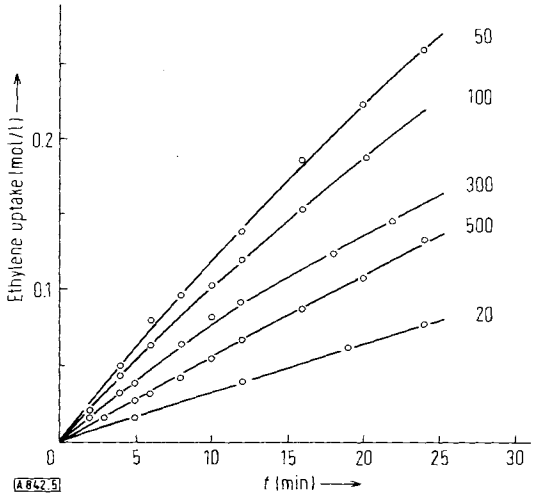


Fig. 5. Polymerization of ethylene with $VO(acac)_2/(C_2H_5)_2AlCl$ in the presence of $(C_6H_5)_3P$, at different ratios Al/V (numbers next to curves). $[V] = 1 \times 10^{-4}$ mol/l; P/V = 6; toluene, 20°C, ethylene pressure = 700 torr.

A look at Table 1 does not provide an immediate explanation for this behavior. The discussion is easier at the higher end of the Al/V scale. From Al/V = 100 upwards there is essentially only V(II) present, which must be the catalyst. In this range the initial rate of polymerization decreases linearly with the ratio Al/V, as shown in Fig. 6. This decrease is best interpreted as a blocking of coordination sites by aluminum alkyl, as depicted in formula *(2)* (Section 2.2.2).

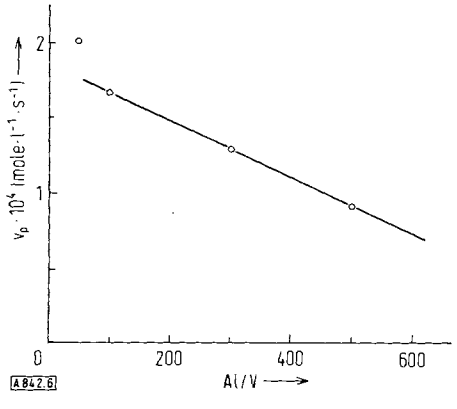


Fig. 6. Initial rate of polymerization V_p as a function of Al/V (taken from Fig. 5).

At Al/V = 50, the rate is higher than could be expected from the linear relationship, although under these conditions only 67% of the vanadium is present as V(II) (Table 1). We may deduce that V(III) is also a catalyst, and even more active than the V(II) species. Why then do we observe such a low polymerization rate at Al/V = 20, where, according to Table 1, we have most of the vanadium present as V(III)? We suggest that the active V(III) species is also a complex with the aluminum alkyl, and that this complex must be formed in an equilibrium reaction. At this relatively low ratio of Al/V there is just not enough aluminum alkyl present to displace the equilibrium sufficiently in favor of the complex.

We may summarize our knowledge concerning the vanadium catalysts as follows: Both V(III) and V(II) species are able to form, with aluminum alkyl, a catalyst for the polymerization of ethylene. V(III) based catalysts are probably more reactive, but less stable at room temperature.

2.3.2. Polymerization with Chromium Systems

A set of polymerization data with the homogeneous system $Cr(acac)_3/(C_2H_5)_2AlCl$ in the presence of $(C_2H_5O)_3P$ and at different ratios of Al/Cr is represented in Fig. 7.

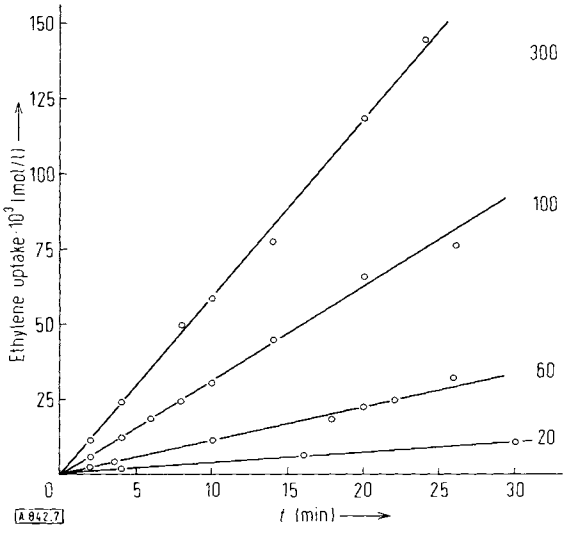
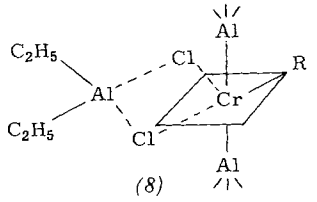


Fig. 7. Polymerization of ethylene with $Cr(acac)_3/(C_2H_5)_2AlCl$ in the presence of $(C_2H_5O)_3P$ at different ratios Al/Cr (numbers next to curves). $[Cr] = 2 \times 10^{-4}$ mol/l; P/Cr = 6; toluene, 20°C; ethylene pressure = 700 torr.

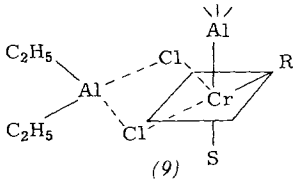
The same system has been investigated magnetically (Fig. 4). A comparison of the two sets of data indicates clearly that the active species is the high spin Cr(II) complex *(7)*, whereas the low spin Cr(II) complex *(6)* predominantly present at Al/Cr = 20 is inactive. It is evident that the acac ligands must be replaced by C_2H_5 and Cl in order to obtain the active species. This exchange not only makes a site available for the coordination of the monomer, but also provides a chlorine "pier" for the activating aluminum bridge (compare the case of titanium[8]).

As mentioned already in connection with the magnetic measurements, the high spin Cr(II) is also soluble in the absence of phosphite at Al/Cr > 200. The rate of polymerization of ethylene, obtained with such a phosphorus-free catalyst under otherwise identical conditions is about

three times higher than with the system containing $(C_2H_5O)_3P$. (Compare Fig. 8, upper curve, with Fig. 7, curve for Al/Cr = 300.) This indicates that different ligands are effective in the two cases. In the presence of phosphite, the two ligands L of the octahedral complex *(7)* are probably $(C_2H_5O)_3P$. Since in the absence of this compound the solubility of the Cr(II) species can be achieved only at very high ratios of Al/Cr, we may conclude that one or two further aluminum alkyl molecules have entered into the coordination sphere of the chromium to maintain it in solution, *e.g.* as *(8)* or *(9)* (with ≥Al = aluminum alkyl, S = solvent, and R = C_2H_5 or growing chain).



(8)



(9)

Since no more Cl ligands are available as piers for bridge bonds, we have to consider direct Al—Cr interaction. (A similar suggestion was put forward by *Wilke et al.*[29] for Al—Ni during the reaction of bis(π-allyl)Ni with $(C_2H_5)_2AlH$.)

Polymerization with phosphite-free systems was further investigated with $(C_2H_5)_2AlCl$ as well as with $C_2H_5AlCl_2$. Three runs are represented in Fig. 8 and described in Table 3. The polymers A and B differ only in the degree of conversion. The polymers have been analyzed by gel permeation chromatography; the molecular weight distributions obtained from these data are given in Figs. 9 and 10.

Polymerization with $(C_2H_5)_2AlCl$ proceeds at a considerably higher rate, and at comparable conversion also gives a higher molecular weight than that observed on polymerization with $C_2H_5AlCl_2$ (see Table 3). This parallels the experience with titanium catalysts[8, 9], and corroborates the assumption that the aluminum alkyl forms part of the catalytic complex. The donor ligand C_2H_5 destabi-

Table 3. Conversion and molecular weights of polymers prepared with $Cr(acac)_3$ catalyst systems in the absence of phosphite. $[Cr] = 2 \times 10^{-4}$ mol/l, Al/Cr = 300, T = 20 °C, ethylene pressure = 700 torr.

Polymer	Al-alkyl	t (min)	Conversion (mol/l)	$M_n \times 10^{-3}$ [a]	$M_w \times 10^{-3}$ [a]	Polymer molecules per Cr
A	$(C_2H_5)_2AlCl$	15	0.29	41.1	635	0.98
B	$(C_2H_5)_2AlCl$	33	0.56	62.5	776	1.23
C	$C_2H_5AlCl_2$	248	0.31	18.1	117	2.4

[a] Determined by gel permeation chromatography.

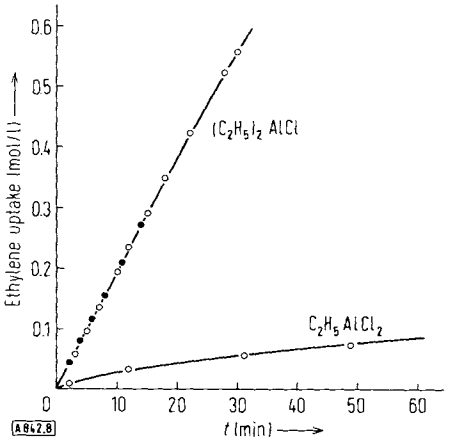


Fig. 8. Polymerization of ethylene with phosphite-free $Cr(acac)_3$ systems. Upper curve: polymer A (●) and polymer B (○); lower curve: polymer C (see Table 3).

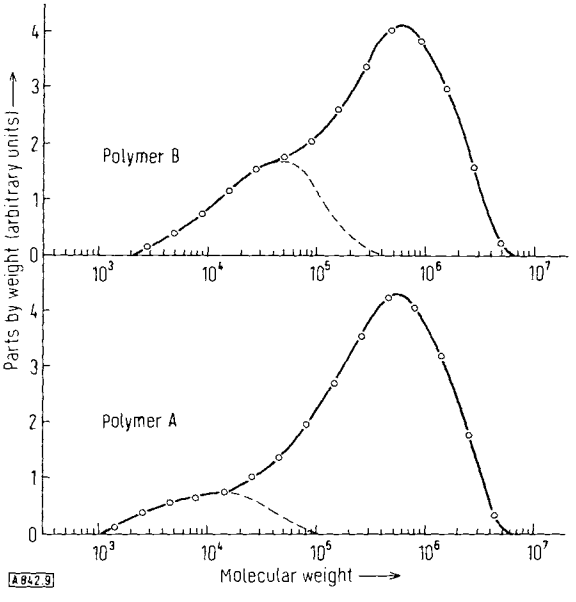


Fig. 9. Molecular weight distribution of polymers A (below) and B as determined by gel permeation chromatography; conversion 0.29 and 0.56 mol/l, respectively (see Table 3).

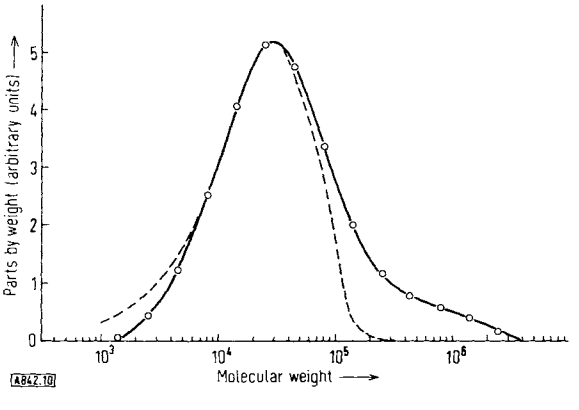


Fig. 10. Molecular weight distribution of polymer C as determined by gel permeation chromatography; conversion 0.31 mol/l (see Table 3).

lizes the metal carbon bond Cr—R (with $R=C_2H_5$ or growing chain) *via* the bridge bond[9], and here perhaps additionally *via* the direct Al—Cr bond [see *(8)* and *(9)*], and thus increases the polymerization rate. The acceptor ligand Cl, on the other hand, withdraws electron density from the transition metal, and in this way increases its ability to abstract β-hydrogen from the growing chain[9b]:

$$\begin{aligned} &Cr{-}CH_2{-}CH_2{-}P \longrightarrow Cr{-}H + CH_2{=}CH{-}P \\ &Cr{-}H + C_2H_4 \longrightarrow Cr{-}CH_2{-}CH_3 \end{aligned}$$

This chain transfer reaction obviously reduces the molecular weight.

Roughly one polymer molecule has grown per chromium center in the systems containing $(C_2H_5)_2AlCl$ (see last column in Table 3), indicating that in these cases the polymerization process proceeds, at least predominantly, *via* a "living polymer" mechanism. That means that neither chain transfer nor termination reactions occur, and the Cr-polymer bond is broken only when the reaction solution is quenched with methanol at the end of the reaction. The increase of the number average molecular weight M_n with growing conversion confirms this view. With $(C_2H_5)AlCl_2$, on the other hand, 2.4 polymer molecules have grown, on average, at every Cr center, confirming the chain transfer process previously mentioned.

The polymers have an extremely broad molecular weight distribution, recalling those normally obtained with heterogeneous catalysts (M_w/M_n: 15.4 for A, 12.4 for B, and 6.4 for C). The gel permeation chromatography diagrams give some additional information concerning this point. In the case of the systems with $(C_2H_5)_2AlCl$ (Fig. 9), the molecular weight distribution curves show (at least) two maxima. The abscissa value of the lower maximum increases roughly proportionally with the conversion, as is usual for living polymers. Although this low molecular weight fraction constitutes only 1—2% of the total weight of the polymer, it contains more than 90% of the polymer molecules. (It was calculated from the GPC data that more than 90% of the molecules of polymers A und B have a molecular weight $<10^5$.) The bulk of the polymer thus consists of relatively few extremely large molecules, which must have grown at different catalyst centers, having a much greater rate constant of chain growth than the centers producing the low molecular weight part.

If one wishes to speculate about the configuration of the two different growth centers, one might suggest structures *(8)* and *(9)*, or perhaps a complex with two solvent ligands as a third possibility. Since aluminum alkyls presumably act as electron acceptors with respect to Cr(II), and the aromatic solvent, on the other hand, as a donor, the solvent-containing structure should be responsible for the high molecular weight part, due to more effective activation of the Cr-carbon bond. Alternatively, one of the structures might sterically (or electronically) hinder the coordination of the ethylene, thus giving rise to a much slower reaction rate.

In the case of the system with $(C_2H_5)AlCl_2$ (Fig. 10), the situation is different. The low molecular weight maximum is much more prominent, and has an approximately "normal distribution", as expected for molecules terminated by chain transfer. (The dotted curve in this figure has been calculated for a normal distribution with the average molecular weight equal to the abscissa value of the low molecular weight maximum of the curve[40].) However, there is also a high molecular weight part which must have grown at different centers.

The experiments with homogeneous chromium systems have shown that the catalyst center is an octahedral Cr(II) species in a weak ligand field (high spin) with a bridge-bonded aluminum alkyl.

The Lewis acidity of these Cr(II) centers, particularly of those prepared with $(C_2H_5)_2AlCl$, is not high enough to cause sufficient chain transfer to control the molecular weight, so that living polymers are obtained, *i.e.* the molecular weight increases with growing degree of conversion.

At least two different catalyst centers are present, the rate constants of which differ by at least an order of magnitude.

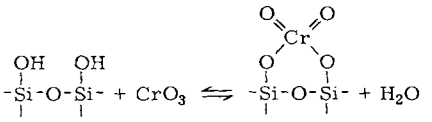
3. Heterogeneous Catalysis

The most important heterogeneous chromium catalyst is that of the Phillips process[2], *i.e.* supported chromium oxide, which works at low ethylene pressure (even at subatmospheric) and temperature (in special cases as low as −40°C). The process was discovered in 1951. In the ensuing years it has been used worldwide and is the dominant commercial process for linear polyethylene. For example, it presently accounts for about two thirds of USA capacity, the remaining third being of the Ziegler type[41].

Perhaps the most impressive description of the discovery of this process is the report of one of the inventors[42]: "Some years ago *W. C. Lanning, J. P. Hogan, R. C. Banks* and I *(A. Clark)* were studying the polymerization of ethylene from refinery stack gases to liquid polymers over nickel oxide supported on silica-alumina, a catalyst discovered earlier at Phillips by *J. A. Reid* and *G. C. Bailey*. We were trying to make motor fuel. But the process made a lot of butylene, giving a total product which was too volatile for motor fuel. Many catalyst modifications were tried in an effort to reduce the volatility. One day chromium oxide was added to the catalyst, and all the ethylene reacted to form high polymer. That solved the volatility problem! It was quickly shown that high polymers could be made without nickel oxide. Then began a gratifying and hectic period when ideas and nature seemed to be cooperating".

The elucidation of the catalytic characteristics and the mechanism of this process has been the subject of numerous papers[43-48]. The catalyst is generally prepared by impregnation of silica or silica-alumina with an aqueous solution of CrO_3. After drying, the finely divided catalyst is activated by fluidizing in dry air at 500—1000°C for several hours. It is then stored in dry air or nitrogen. A recent careful study by one of the inventors[48] has revealed that the chromium trioxide forms a chromate *(10)* with the silanol groups of the carrier surface.

During the activation process (500—1000 °C, streaming dry air) the equilibrium is shifted to the right and water is removed. The formation of surface chromate accounts for



(10)

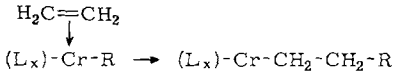
the ability of silica to stabilize Cr(VI) far above the decomposition temperature of CrO_3. Thus, more than 90% of the chromium can be present as Cr(VI) after the activation period (provided overloading with Cr has been avoided). If ethylene is then brought in contact with the catalyst the Cr(VI) behaves in the usual way as a strong oxidizing agent. In a redox reaction the true catalyst species is produced in form of a low-valent chromium center and the hydrocarbon undergoes oxidation. The oxidation products poison the catalyst centers. As a consequence, polymerization starts with an induction period. In time, however, ethylene displaces the poisoning substances and the final polymerization rate is reached. The induction period can be avoided if the catalyst is reduced with H_2 or CO at 250—400 °C before the admission of ethylene. CO treatment is preferable, since with H_2 water is formed which decomposes the chromate bonds in *(10)*; the free CrO_3 then decomposes to inactive Cr_2O_3. After reduction with CO, the catalyst must be flushed with N_2 at 300—400 °C in order to eliminate excess CO which would otherwise block all coordination sites.

The actual valence state of the reduced chromium in the active center has been the object of conflicting views. Cr(III) has been proposed with the argument that valences intermediate between Cr(VI) and Cr(III) are unstable and have defied attempts at separation[44]. It can be seen from the work with homogeneous catalysts reported in the last section that this reasoning is not sufficient [Cr(II) being the active species there].

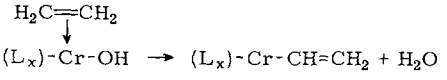
Other workers favored Cr(V) in view of an ESR signal at $g = 1.97$ exhibited by the solid catalyst and ascribed to Cr(V)[43,45]. The polymerization activity was found to be proportional to the intensity of this signal[43]. This correlation was established with the ESR signal given by the catalyst before the polymerization reaction has started. Later on, however, it was discovered that the signal declines appreciably during the polymerization process while the activity appears to be sustained[46]. Thus the ESR signal could be, at best, due to a precursor of the active site.

Finally, *Krauss* and *Stach*[47] reported recently that the average oxidation state of the chromium in a CO reduced catalyst may well approach the value of two under optimal conditions, and that the polymerization rate increases with the fraction of Cr(II) for catalysts with average oxidation state between two and three (20 °C, 1 atm.). They also proved the presence of Cr(II) by a characteristic absorption in the reflection spectrum at 725 nm, and this not only in CO-reduced, but also in ethylene-treated catalysts. Thus it was reasonably concluded that Cr(II) is the essential part of the active centers.

For the initiation of polymerization it appears necessary that this Cr(II) center has a ligand R able to attack the first coordinated ethylene molecule:



Under the usual conditions of reduction of the chromium, with ethylene itself or with H_2 or CO, R might well be a hydrogen or an OH group. It has also been proposed that the first step might be an elimination of water from an OH group and hydrogen from ethylene:



No effort has been reported to clarify this open question by analysis of low conversion material.

Heterogeneous vanadium systems have considerably less importance. Patent literature is abundant, but no detailed mechanistic study of the polymerization process has come to our attention. Perhaps a recent reference concerning vanadium oxide as a highly active catalyst for the polymerization of ethylene[49] will turn out to be important in the future.

4. Comparison between Homogeneous and Heterogeneous Catalysts

Although Cr(II) appears to be the active valence state in homogeneous as well as in heterogeneous catalysts, there are considerable differences between these two kinds of systems which require further discussion.

Primarily, no aluminum alkyl is necessary in the Phillips catalyst to reduce the chromium and to stabilize the active valence state. Furthermore, the heterogeneous catalyst is far more reactive (considerably more monomer is converted per active site and unit time, see Table 4). Finally, a great number of polymer molecules grows per minute on each active site of a Phillips catalyst, indicating a strong chain transfer reaction, confirmed by the fact that each polymer molecule has one vinyl and one methyl end group[48]. In the homogeneous systems, on the other hand, no essential chain transfer but living polymers were found.

The heterogeneous and homogeneous systems are compared in Table 4. To make the data comparable, the polymerization rate and the rate of chain transfer are given per active site and per minute.

Although the data of Table 4 are obtained at different temperatures, the higher activity of the Phillips catalyst, for both growth and chain transfer, is obvious.

If we admit that the active species in the heterogeneous and the homogeneous catalysts both contain Cr(II), we must make the ligand environment of the Cr(II) centers responsible for the differences.

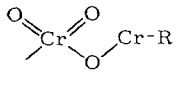
Table 4. Comparison of heterogeneous and homogeneous Cr catalyst. Ethylene pressure roughly 1 atm.

T (°C)	Catalyst system	Polymerization rate [a]	Chain transfer rate [b]	Ref.
95	Phillips (1% Cr on SiO_2)	1.2×10^5	168	[48]
20	$Cr(acac)_3$/ $(C_2H_5)_2AlCl$	100	$\simeq 0$	Polymer A, Table 3
20	$Cr(acac)_3$/ $C_2H_5AlCl_2$	15	2.3×10^{-2}	Polymer C, Table 3

[a] Monomer units grown per active site per minute.
[b] Chain transfer steps per active site per minute.

The rate-determining step for chain growth appears to be the coordination of the ethylene to the metal center. A Cr(II) center at a heterogeneous catalyst surface is presumably coordinately unsaturated. This has been deduced by *Hogan*[48], who reported that the Phillips catalyst trimerizes acetylene to benzene at a high rate, indicating space for the simultaneous coordination of three acetylene molecules around a single Cr site. The homogeneous center, on the other hand, can achieve the preferred hexacoordination in a variety of ways (aluminum alkyls, solvent). Presumably, the "free coordination site" [see formulas *(7)*, *(8)*, and *(9)*] is not really free on average, but one weakly bonded ligand has to be replaced by ethylene in an equilibrium reaction. This would explain the large differences in polymerization rate.

The ability to cause chain transfer (β-hydrogen abstraction) is governed by the electron affinity of the metal center. (This has been shown experimentally in the case of titanium catalysts[9a].) In the homogeneous systems the aluminum alkyl ligands have not sufficiently strong Lewis acid character to increase the electron affinity of the Cr(II) center to such an extent as to cause considerable chain transfer, although a significant difference is to be noted in the electron-withdrawing effect of the two aluminum alkyls ($C_2H_5AlCl_2 > (C_2H_5)_2AlCl$, see Tables 3 and 4). For the Phillips catalyst, however, we have to look for an environment much more electron withdrawing than that provided by the aluminum alkyls. The choice is not very broad: either part of the chromium has survived the reduction process in a higher valence state and forms oxygen bridged surface compounds with the Cr(II) centers, *e.g.*



or the supporting material acts in some way or other as a strong Lewis acid, withdrawing electron density from the Cr(II) centers. Unfortunately, no systematic data are available which would correlate the number average molecular weight of the polymer, under otherwise identical conditions, with the average oxidation state of the chromium (*e.g.* after different times of CO treatment) and with the acidity of the support. Thus the question of the environmental conditions favoring the β-hydrogen transfer reaction in the Phillips catalyst must also remain open.

In conclusion we wish to express our hope that the present paper may help to emphasize the basic similarities of homogeneous and heterogeneous polymerization reactions. We feel that, as in the case of titanium, the study of soluble systems can also help to provide a better understanding of the heterogeneous catalysts, allowing the establishment of general principles of common application.

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Synthesis of Naturally Occurring Polypeptides, Problems of Current Research[**]

By Erich Wünsch[*]

The synthesis of naturally occurring polypeptides has recently again become a center of interest. It therefore seems appropriate to make a critical appraisal of the present state of research, and at the same time to try to eliminate much of the element of chance from the solution of the problems that face us. An attempt will be made to group the preparation methods commonly used in the past into four strategies, to point out their advantages, and to uncover their disadvantages. The ultimate aim in the synthesis of naturally occurring peptides must always be a true, clean synthesis.

1. Introduction

After its beginning with the synthetic preparation of oxytocin[1], the synthesis of naturally occurring polypeptides rose to a peak, and also came to a temporary halt, with the synthesis of ACTH (adrenocorticotropic hormone) by *Schwyzer et al.*[2]. The rapid further progress since that time has taken four directions:

Strategy I, the conventional synthesis with maximum masking of the side-chain functions of polyfunctional amino acids (referred to hereafter as third functions), by which the total syntheses of glucagon[3,4] and of calcitonin[5,6] were achieved. In the synthesis of glucagon, all the third functions were masked except the ω-amide groupings of aminodicarboxylic acids. *Akabori*[7], *Weygand*[8], *Chillemi*[9], and more recently *Geiger*[10] and their coworkers have carried out syntheses in which this ω-amide function was also protected.

Strategy II, the conventional synthesis with minimum masking of the third functions of polyfunctional amino acids. It is based on systematically controlled linkage with the aid of *N*-carboxylic acid anhydrides. *Denkewalter, Hirschmann et al.*[11,12] have shown that only the ω-amino and mercapto functions must be blocked.

Any intermediate stage (as far as masking of the third functions is concerned) between the two extremes of the conventional peptide synthesis is naturally possible; the work of *K. Hofmann*[13] on the ribonuclease synthesis is characterized in particular by relatively slight masking of the third functions.

Features common to both conventional synthesis strategies, except in a few cases, are:

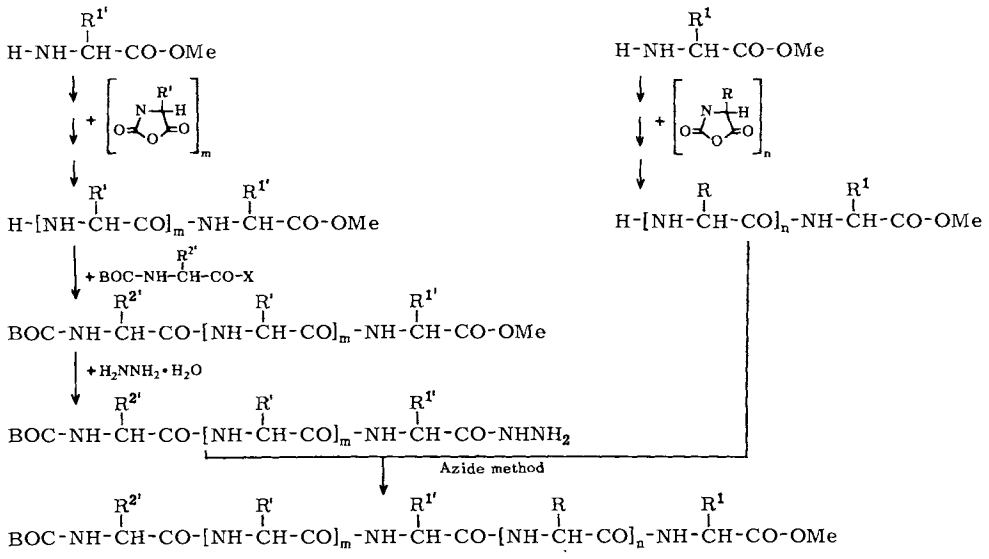
1. The initial construction of large peptide fragments,
2. the subsequent linkage of these fragments to form larger units. In view of the technique used, this is possible only by the azide method in strategy II (Scheme 1).

Strategy III, the "solid-phase synthesis", which was launched by *Merrifield*[14,15], and of which there are a number of variants. In all solid-phase syntheses (except the methods used by *Letsinger*[16] and more recently by *Merrifield*[17][*]), the C-terminal amino acid of the peptide is masked by attachment to a polymer. The peptide sequence was originally built up in steps in all the solid-phase methods. The obvious aim of both the older "Merrifield method"

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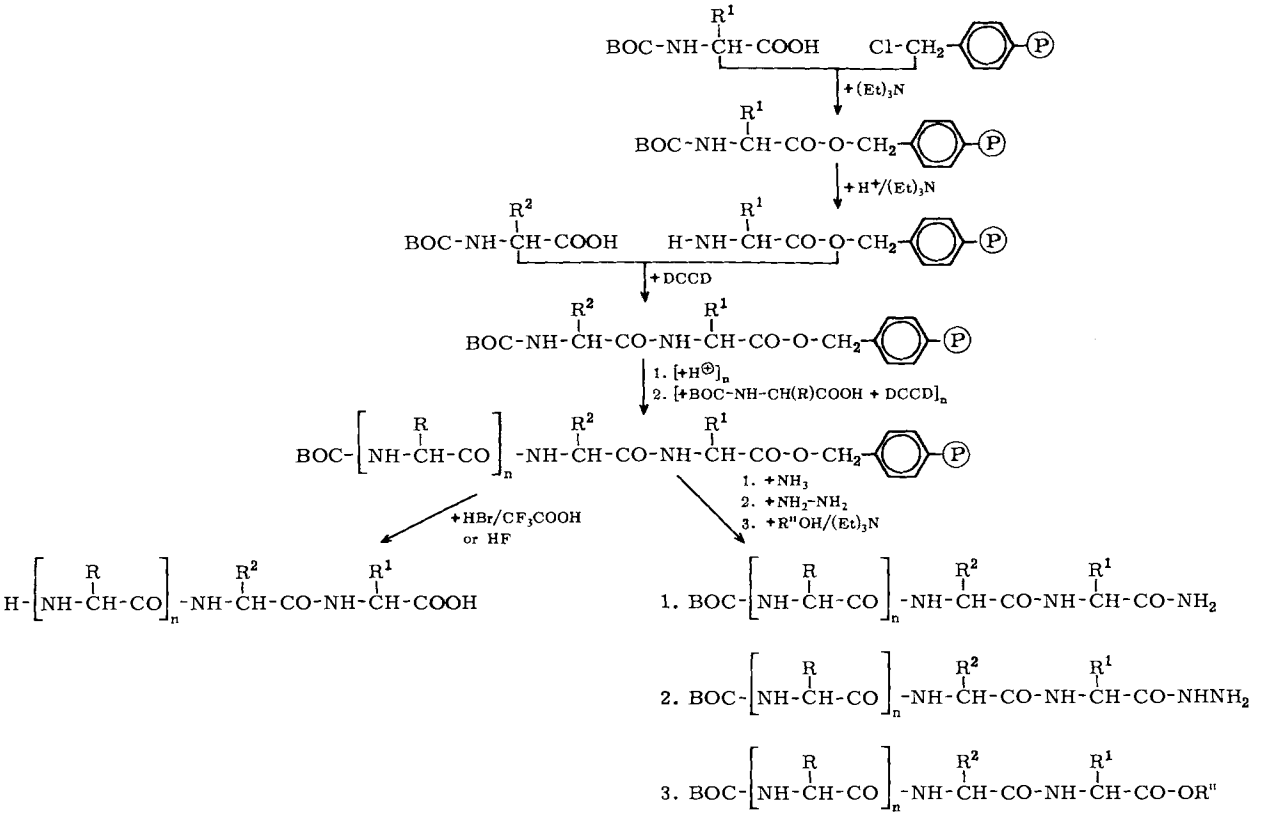
[*] In these methods [16, 17], the N-terminal amino acid is attached to the polymer.



Scheme 1. Strategy II using the *N*-carboxylic acid anhydride method. Me = methyl, BOC = *tert*-butyloxycarbonyl, X = succinimidyl. Side-chain protection for lysine: N_ε-benzyloxycarbonyl; side chain protection for cysteine: *S*-acetamidomethyl.

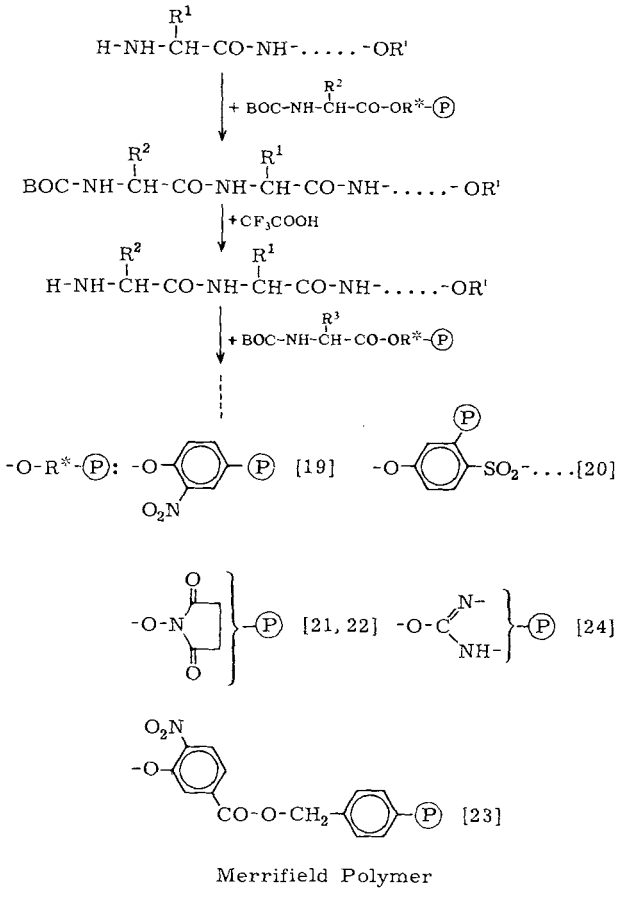
and the "Shemyakin method"[18] is the synthesis of the complete sequence (Scheme 2).

Strategy IV, the "polymer reagent synthesis", which was introduced by *Katchalsky*[19] and *Wieland*[20] on the basis of polymer nitrophenyl esters and polymer sulfonylphenyl esters, and was recently carried on by *Blout*[21] and *Fridkin*[22] with polymer hydroxysuccinimide esters, by *Panse* and *Laufer*[23] with modified polymer nitrophenyl esters, and (even earlier than these authors) indirectly by *Frankel*[21] with the use of polymer carbodiimides. The feature common to all these syntheses is the conversion of acylamino acids or peptides into polymer-activated carboxyl



Scheme 2. *Merrifield*'s solid-phase synthesis. All third functions except the ω-amide function must be masked. (P) = polymer, DCCD = dicyclohexylcarbodiimide, Et = ethyl, BOC = *tert*-butyloxycarbonyl.

derivatives and their linkage to amine components of various types and sizes (Scheme 3).



Scheme 3. Strategy IV. Bottom: examples of the group —O—R*—(P). (P) = polymer, BOC = *tert*-butyloxycarbonyl.

2. Critical Discussion of the Four Synthesis Strategies

2.1. Strategy I

The conventional synthesis with maximum use of protective groups allows the synthesis of peptide fragments, and recently also the successive linkage of these fragments to form the complete unit, with almost total avoidance of by-products; since the problem of linkage without racemization may now be regarded as having been largely solved[25,26], this principle appears to merit the comment "very good" for the synthesis of peptide sequences containing up to 30 amino acid residues. For longer sequences, the solubility of the peptide chain presents considerable difficulties in strategy I; depending on the nature of the peptide sequence to be synthesized, therefore, the maximum sequence length that may be expected by this method at present is in the region of 30—50 amino acid residues.

2.2. Strategy II

The conventional synthesis with minimum masking of the third functions is not reliable as regards freedom from by-products in the synthesis of the first partial sequences; one is therefore more or less forced to interrupt the stepwise synthesis of the peptide fragments with *N*-carboxyamino acid anhydrides at intervals to purify a partial sequence. For the further synthesis the fragments, which are obtained as *N*-acylpeptide esters, must, with the exception of the C-terminal fragment, be converted into *N*-acylpeptide hydrazides[27–29]; it remains to be seen whether the technique developed for this purpose by *Denkewalter, Hirschmann, et al.*[11] generally proceeds without side reactions. These *N*-acylpeptide hydrazides are then linked successively to the C-terminal fragment by the azide technique[27–29] (cf. Scheme 1). This restriction to the azide method for the linkage of the fragments must be seen as a distinct disadvantage of strategy II; it has been known for a long time that the azide method is not all that one might wish as far as yield is concerned, and that it is subject to side reactions as a result of an azide-isocyanate rearrangement. Above all, it is practically impossible to separate urea derivatives formed in these reactions from the "correctly linked" peptide sequences.

This method has undisputable advantages in three respects: the ease and cheapness of preparation of the linking materials (*N*-carboxyamino acid anhydrides);

the very high reactivity of the *N*-carboxyamino acid anhydrides, and hence the relatively fast linkage;

the better solubility properties of the fragments prepared by this principle (as compared with those of the fragments prepared by strategy I).

2.3. Strategy III

The most surprising features of the solid-phase synthesis in its many variations are the idea itself, its simplicity, and finally the possibility of the automation or mechanization of peptide syntheses. On closer examination, however, the solid-phase synthesis exhibits "inborn defects", in the build-up technique on the one hand, and in the present inadequacy of analytical methods on the other.

1. In the stepwise addition of *N*-acylamino acids ("head components") to the amino component, which is attached by its carboxyl function to a suitable polymer, the desired *N*-acylaminoacylation can be achieved quantitatively only with an excess of active head component (5 moles or more of the head component are often used). This technique, particularly when "anhydride-like" activation stages are used, presents considerable danger of *N*-acylaminoacylation of peptide linkages[30], with all the possible consequences of this "diacylamine formation", such as chain shortening[31] and chain lengthening[32] (cf. Scheme 4).

2. As was indicated under 1, the solid-phase synthesis is based on a quantitative reaction of the amino component, and hence on 100% unmasking of the *N*-acylpeptide derivatives formed. Definite quantitative information on these two reaction steps is at present possible only after removal of the peptide chain from the polymer (cf. 4), and with an uncertainty of ±2% by the analytical methods that are currently available. This uncertainty is too great for the assessment of solid-phase syntheses of peptides containing more than 15 amino acid residues; it should

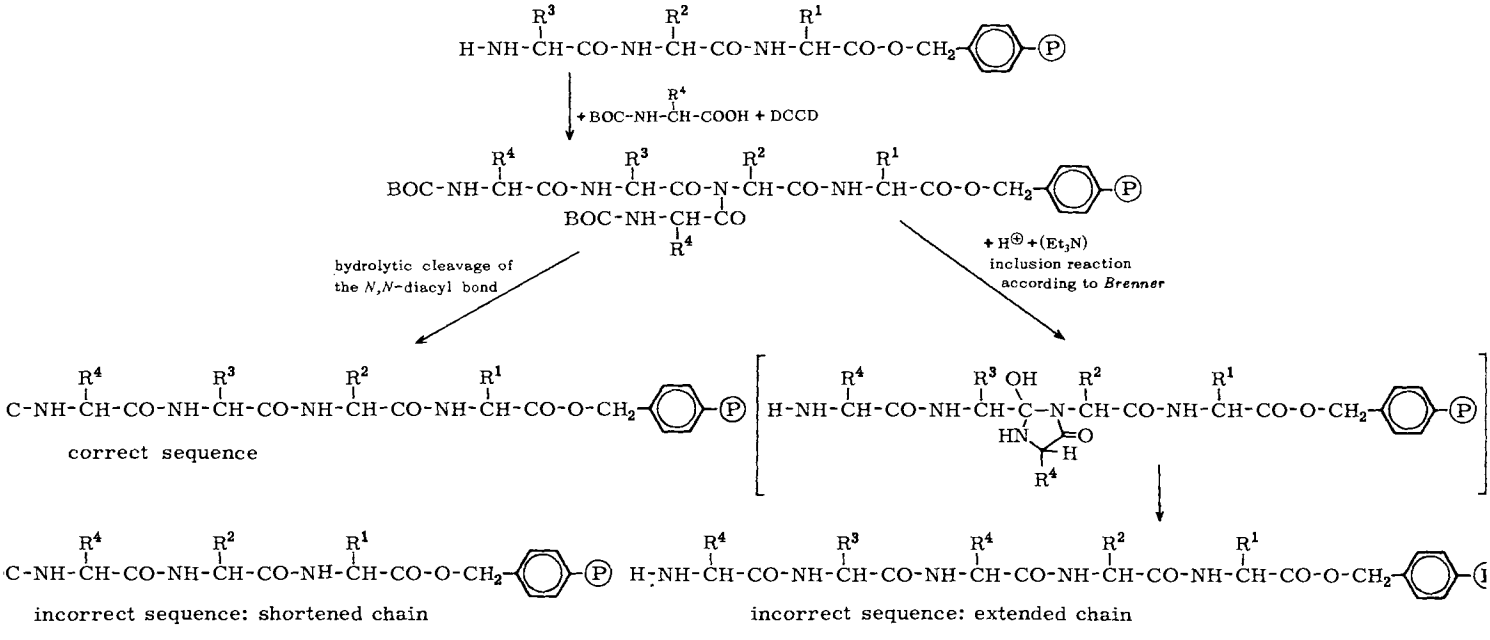
be of the order of $\pm 0.1\%$. The time required for such a determination nevertheless remains the same; this considerably detracts from the simplicity of the solid-phase synthesis.

Interesting direct determinations of unreacted *N*-α-amino groups in the reaction mixture have been described. However, both the normal Edman degradation followed by mass-spectrometric dilution analysis[33] or scintillation analysis using radioactively labeled isothiocyanates[34] and has been random, a consequence of the preparation method. This means:

inevitable differences in swellability and pore size between individual charges of support material;

a danger of steric hindrance effects as the peptide synthesis progresses when the "loading density" is too high;

doubtful applicability of "equivalent analysis" for the determination of the peptide-chemical conversion in accordance with 2.



Scheme 4. Strategy III: Undesirable *N*-aminoacylation of a peptide linkage and subsequent reactions. (P) = polymer, DCCD = dicyclohexylcarbodiimide, Et = ethyl, BOC = *tert*-butyloxycarbonyl.

the well-known spectrophotometric analysis of a 2-hydroxy-1-naphthaldehyde reaction[35] are based primarily on chemical reactions of these residual free amino groups without definite knowledge of the proportion that has reacted. These determination methods are therefore fundamentally subject to the same "uncertainty" as the reaction to be determined.

3. The solid-phase synthesis also depends on the swellability or solubility of the amino component-polymer with or in solvents. As a physical constant, the swellability or solubility must initially be a property of the polymer. During the growth of the high molecular weight peptide chains, however, this physical constant will be increasingly influenced by the peptide chain; from experience in conventional syntheses with maximum use of protective groups (strategy I), it may be expected that the swellability or solubility of the complex will be determined by the peptide, and not by the polymer, at a chain length of 30—50 amino acid residues. It will obviously then be necessary to take the "loading" of the polymer into account as an additional factor.

(The diffusion of the head component, which is closely connected with the swellability of the peptide-polymer, is discussed in Section 2.4.)

4. The particle sizes of the polymers used in all the solid-phase syntheses carried out so far have been relatively arbitrary, and the distribution of the attached groupings

The "inborn defects" mentioned under 1 to 4 must be eliminated at all costs if the solid-phase synthesis is to become an ideal method, particularly for the synthesis of naturally occurring peptides.

2.4. Merrifield Technique

The much-mentioned "Merrifield technique" (cf. Scheme 2) as described by *Merrifield*, *Stewart*, and *Jernberg*[36,37] is a special variant of the solid-phase synthesis; it therefore possesses the "general inborn defects" mentioned above. However, it also has other peculiarities that require critical examination, simply because the "Merrifield technique", particularly in its automated or mechanized form, has become more widely used than other methods in many laboratories in view of the speed, extreme simplicity, and complete mechanizability that are ascribed to it. The main features of the "Merrifield technique" are:

1. The attachment of the C-terminal amino acid to a polymer with formation of a benzyl ester. Except in a few cases, this is achieved by reaction of *N*-BOC-amino acids with a chloromethylated phenyl polymer (polystyrene copolymer with 2% of divinylbenzene) in the usual manner.

2. After removal of the N-protective group, *N*-BOC-amino acids are incorporated stepwise into the amino component-polymer by the carbodiimide method or the nitrophenyl

ester method[38]. (Masking of the third function is necessary in polyfunctional amino acids.) This stepwise incorporation is carried out at fixed time intervals (*e.g.* 2 or 4 hours) and without purity checks on the intermediates.

3. The "unchecked" synthesis of the peptide chain is followed by removal from the support material by proton solvolysis of the benzyl ester linkage *e.g.* with hydrogen bromide/trifluoroacetic acid or anhydrous liquid hydrogen fluoride[39,40]; benzyl-based third function masking groups, with the exception of the N^{im}-benzyl grouping, are removed at the same time (N^{im} = N-1 in the imidazole part of histidine).

Removal from the solid support can also be achieved by ammonolysis[38] or hydrazinolysis[41] with simultaneous peptide amide or peptide hydrazide formation or with transesterification by base-catalyzed alcoholysis (racemization?), which leads to *e.g.* peptide methyl esters[42], though success is assured only if the sequence synthesized contains no aminodicarboxylic acid or aminodicarboxylic acid ω-amide residues or peptide linkages that can be broken by these procedures. The cleavage of the benzyl ester linkage of the polymer by hydrogenolysis or by alkaline hydrolysis is probably of little significance.

This synthesis method has several sources of error:

Regarding 1: The reaction of the benzyl groups of the polymer is incomplete; residual benzyl chloride or benzylammonium groupings are quite likely to cause side reactions in the course of the synthesis.

Loffet[43] has recently suggested the use of tetramethylammonium hydroxide as the base to avoid the formation of quaternary salts on the polymer.

should generally be given to this method for the preparation of the amino component-polymer[38,44].)

Regarding 2: The stepwise incorporation of *N*-BOC-amino acids at fixed time intervals is probably one of the main sources of error in the "Merrifield technique". Apart from the above-mentioned possibility of diacylation of the peptide linkages, limitation of the time available for the linkage step, even with a large excess of the head component, is unsuitable for quantitative formation of the peptide linkage.

Prediction of the reaction rates is impossible at present, and almost certainly will not become possible in the near future, since these depend not only on the two amino acids being linked but also (particularly in the solid-phase synthesis) on the size and nature of the amino component polymer, *i.e.* the conformation of the peptide chain including the solid support[34], as well as on the rate of diffusion of the head component (and possibly also of dicyclohexylcarbodiimide) in the swollen amino component-polymer.

Klostermeyer[45] had the following to say regarding the latter phenomenon: "This possibility was surprisingly never considered during the development of the method, as Professor *Merrifield* confirmed in a personal discourse at the IXth European Peptide Symposium at Orsay in April 1968.

The diffusion effect naturally has a considerable bearing on the usefulness of the Merrifield synthesis, which does not satisfy the claim that it is universally applicable and mechanizable. This would be possible only if each reaction step proceeded quantitatively under standardized conditions.

Table 1. Determination of free amino groups during the synthesis of $(Leu\text{-}Ala)_6$ [48].

Amino acid sequence	Ala	Leu	Ala	Leu	Ala	Leu	Ala	Leu	Ala	Leu	Ala	Leu
Coupling step	1	2	3	4	5	6	7	8	9	10	11	
Free amino groups after cleavage of protecting group (2 mmol = 100%)	2.05	1.96	2.05	2.04	1.92	1.85	1.85	1.52	1.55	1.08	1.01	
Free amino groups after the 1st reaction in mmol	0.01	0.08	0.08	0.08	0.48	0.09	0.77	0.137	0.79	0.29	0.535	
in %	0.5%	4%	4%	4%	25%	5%	42%	9%	51%	27%	53%	
Free amino groups after the 2nd reaction in mmol	0	0	0.01	0.01	0.08	0.037	0.388	0.076	0.543	0.26	0.23	
in %	0%	0%	0.5%	0.5%	4%	2%	21%	5%	35%	24%	23%	
Free amino groups after the 3rd reaction [a] in mmol							0.388			0.26	0.21	
in %							21%			24%	21%	
Free amino groups after the 1st acetylation in mmol					0.388		0.037		0.052	0.19		
in %					0.8%		2%		3.5%	17.5%		
Free amino groups after the 2nd acetylation in mmol										0.104		
in %										9.6%		

[a] Reaction time 8 hours.

Methionine- and N^{im}-benzylhistidine-benzyl ester polymers are obtainable *only* by esterification with the hydroxymethyl solids, residual free hydroxyl groups then being "neutralized" by esterification with acetic anhydride. (Preference

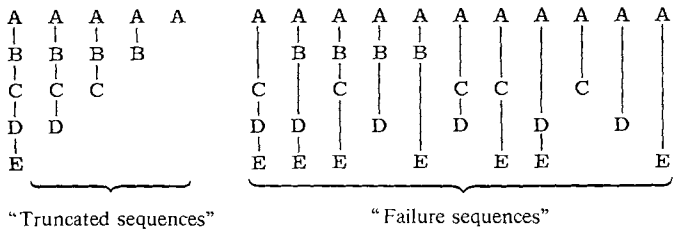
However, a diffusion-controlled reaction depends *inter alia* on the pore size of the support, which not only differs from charge to charge of the starting material but also varies from step to step during the synthesis. It is therefore funda-

mentally impossible to program the various steps of a large synthesis in advance in such a way that the outcome is certain. To make the scope of the method more general, it would be necessary to use a true automatic synthesis system with built-in monitoring of the individual steps, the analytical requirements for which cannot be satisfied."

For these reasons the reaction rates must be determined afresh for each individual case[33,46,47]. This is shown by an investigation by *Hagenmaier*[48] (cf. Table 1):

In the synthesis of the dodecapeptide $(Leu\text{-}Ala)_6$, the linkages of BOC-alanine and BOC-leucine in positions 7 and 10 proceed in yields of only 79 and 76%[*] respectively, even after repetition of the reaction three times with a total reaction time of 12 hours (according to *Weygand*[33], this is more likely to give maximum yields than a single reaction for longer periods).

This necessarily leads to truncated sequences if no further reaction occurs on the unreacted amino groups, while failure sequences[**] are formed if these groups react in the later stages of the synthesis (cf. Scheme 5).



Scheme 5. Synthesis of the pentapeptide A-B-C-D-E; unwanted sequences.

The order of magnitude of the failure-sequence component has been demonstrated by *E. Bayer et al.*[50] *e.g.* for a relatively simple solid-phase synthesis of $(Ala\text{-}Phe)_6$. At least 9.3% of phenylalanylphenylalanine was found as a failure sequence by the partial hydrolysis technique.

Regarding 3: The use of hydrogen bromide/trifluoroacetic acid for removal of the synthesized peptide chain is a relatively severe treatment, which *e.g.* the indole system in tryptophan does not survive without extensive damage. Moreover, the pronounced accumulation of benzyl cations during this operation may lead to benzylation reactions, which cannot always be suppressed by "cation interceptors" if certain steric requirements are satisfied. Benzyl-based third function masking groups, *i.e.* protective groups for the ω-carboxyl, ω-amino, and hydroxyl functions, are simultaneously removed, and this usually rules out any intended "part-sequence synthesis". However, the other third function masking groups used in the "Merrifield technique", *i.e.* the nitro or tosyl group on the guanido function of arginine, the *S*-benzyl masking of cysteine, and the N^{im}-benzyl protective group in histidine are not attacked. The removal of the last two masking groups from cysteine and histidine (and of the N_ω-tosyl protective group from arginine) with sodium in liquid ammonia is not very successful[51–54]; it is unsatisfactory from the standpoint of the method.

Other *S* and N^{im} derivatives of the two amino acids have been adopted from the conventional synthesis, according to the various authors[55–58], sometimes successfully and sometimes unsuccessfully. The prospects are probably best for the *S* and N^{im} protective groups that are stable under the conditions of the removal of the peptide chain from the supporting resin[59–61].

The removal of the peptide chain from the support with liquid hydrogen fluoride at 0 °C, though more promising, is "very expensive" according to *Weber*[56]. In addition to the rupture of the polymer benzyl ester linkage and the removal of all benzyl-based and *tert*-butyl-based *N* and *O* protective groups, the nitroguanido and *S*-methoxybenzyl masking groups are also removed[39]. N^{im}-Benzyl, N^{im}-dinitrophenyl, 4-nitrobenzyl ester, and *S*-alkylthio groupings are reported to be resistant to hydrogen fluoride; the indole system of tryptophan also appears to be unaffected[62].

To summarize the situation, therefore, the "Merrifield technique" in its present form is unsuitable for the satisfactory synthesis of higher natural peptides (with more than 15 amino acid residues). The product isolated, even after purification operations, is always a mixture of peptides, and cannot satisfy the purity criteria of a successful synthesis. The low biological activities of higher naturally occurring polypeptides synthesized so far by this technique[63,64] even make it doubtful whether the technique can be used to confirm a proposed structure.

The question whether the synthesis of peptide fragments containing 10—15 amino acid residues in accordance with the existing principles of the "Merrifield technique" is possible from case to case will be left unanswered for the present.

2.5. Strategy IV

There is little information available at present regarding the use of the polymer reagent synthesis for the preparation of naturally occurring polypeptides[65]; no final judgment can therefore be made as yet.

It must be pointed out in a critical examination that the use of polymer derivatives to activate the carboxyl compound is probably limited by steric problems. This may be of decisive importance in the synthesis of naturally occurring polypeptides.

3. Outlook

It would be unjust to criticize the four principles for the synthesis of naturally occurring polypeptides without offering suggestions as to how the disadvantages could be overcome and how the advantages might be developed further.

[*] According to indirect determination of free amino groups (*Dorman* [49]), the reliability of which may be doubtful. However, the conversions of 19 and 14.4% on acetylation with acetic anhydride confirm a high content of unreacted material (cf. Table 1).

[**] These failure sequences may naturally also result from "diacylamine formation", cf. Section 2.3 and Scheme 3.

3.1. Suggestions for Strategy I

The conventional synthesis with maximum use of protective groups will allow the preparation of naturally occurring polypeptides with more than 50 amino acid residues only if *e.g.* the solubility of the peptide chains synthesized can be considerably improved.

Our investigations on glucagon had shown that the presence of arginine residues protected by protonation considerably increases the solubility of the synthesized fragments in the common solvents[66]. It has now been found in a recent secretin synthesis that the solubility of the secretin fragment 12—27 is influenced to such a degree by the presence of four protonated arginine residues that specific purification of the hexadecapeptide amide derivative L-arginyl-(hydrobromide)-L-leucyl-L-arginyl(hydrobromide)-L-aspa-raginyl(β-*tert*-butyl ester)-*O*-*tert*-butyl-L-seryl-L-alanyl-L-arginyl(hydrobromide)-L-leucyl-L-glutaminyl-L-arginyl(hydrobromide)-L-leucyl-L-leucyl-L-leucyl-L-glutaminyl-glycyl-L-leucyl-L-valinamide hydrobromide is possible by gel filtration on Sephadex G-15 in aqueous media, and that the reaction of this peptide with carboxyl components is possible *e.g.* in dimethylformamide[67].

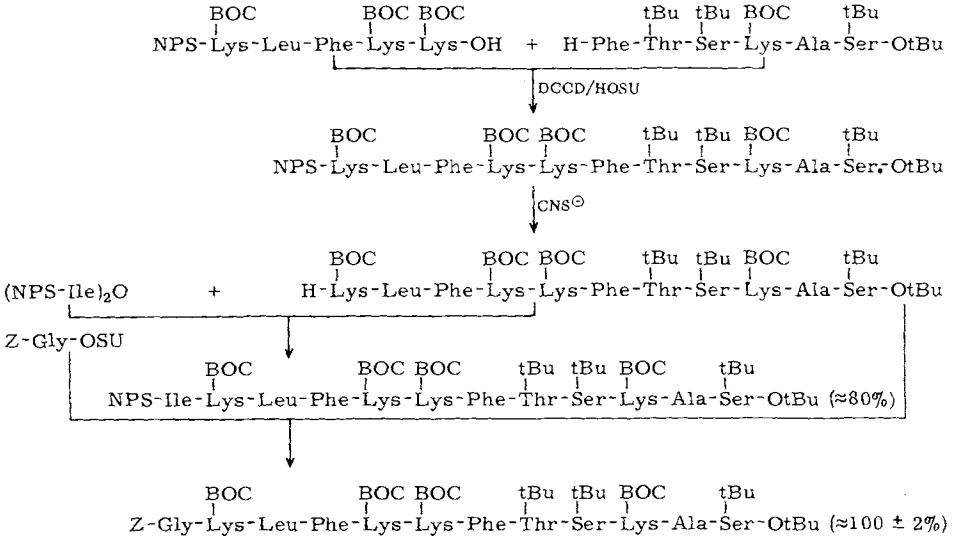
This result led us to hope for a considerable improvement in the solubility of synthesized peptide chains through the use of "bifunctional" protective groups; for example, one line of investigation will be the attempted provision of "artificial" arginine functions in the peptide, with the ultimate aim of achieving a synthesis analogous to the secretin synthesis mentioned.

fd coat protein monomer (49 amino acids) indicate that this is quite feasible. A tridecapeptide derivative of the sequence 37—49, swollen in dichloromethane, was successfully made to react with head components in accordance with the principle of the solid-phase synthesis; the reaction proceeded almost quantitatively with benzyloxycarbonyl-glycine hydroxysuccinimide ester, whereas only about 80% reaction was achieved with the symmetrical anhydride of nitrophenylsulfenylisoleucine, though there were still free, *e.g.* acylatable, amino groups present (cf. Scheme 6)[68].

3.2. Suggestions for Strategy II

The conventional synthesis with minimum masking of third functions has so far been used only by *Hirschmann et al.*[27-29,69,70] in experiments on the synthesis of ribonuclease S, or more precisely the S-protein; this lack of general experience makes a critical evaluation difficult. Two possibilities should, however, be considered for the further development of this synthetic principle:

The synthesis of fragments by the acyl hydrazide method described by *K. Hofmann*[71], which avoids a subsequent hydrazinolysis, and the replacement of the azide method for the combination of the fragments by other linkage methods that proceed without racemization[72]. However, a compromise would then undoubtedly be necessary between masking and nonmasking of the third functions. This would mean there is only one conventional synthesis principle, of which strategies I and II are limiting cases.



Scheme 6. Synthesis of the sequence 38—49 of phage fd coat protein. BOC = *tert*-butyloxycarbonyl, NPS = *p*-nitrophenylsulfenyl, tBu = *tert*-butyl, HOSU = hydroxysuccinimide, Z = benzyloxycarbonyl, DCCD = dicyclohexylcarbodiimide.

A second possibility would be to make use of the substantial insolubility of synthesized peptide fragments of the C-terminal sequence by using these insoluble fragments as their own supports for a solid-phase synthesis. Two synthetic principles would thus be combined. Experiments carried out in my laboratories on the synthesis of the phage

3.3. Suggestions for Strategy III

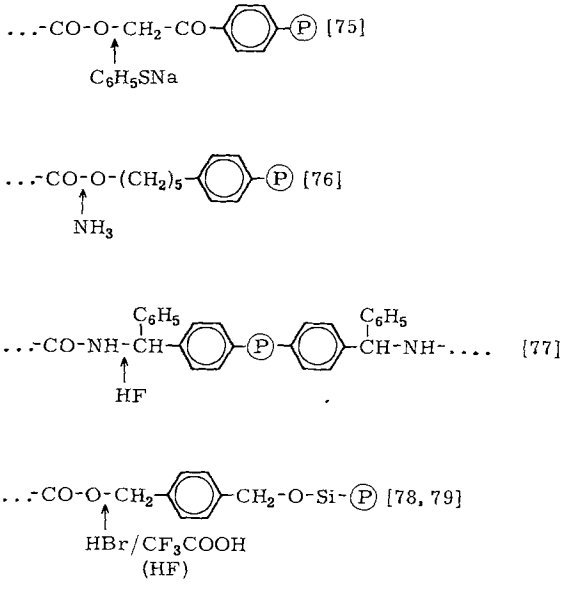
The recognition of the shortcomings and undesirable phenomena associated with the solid-phase synthesis has led to a search for improvements both of the principles of the method and of the analytical determination methods:

1. variation of the "attachment grouping" with a view to obtaining improved removal of the peptide chain from the support and shorter reaction times, which depend on diffusion;

2. modification of the reaction procedure to achieve improvement of the nucleophilic reaction step or correction of the first reaction;

3. extension of the analytical determination methods for the various stages of the synthesis to ensure an uncertainty of $\pm 0.1\%$.

Regarding 1: The relative ease of nucleophilic cleavage of the peptide phenacyl ester linkage[73,74] was used by *Weygand*[75] for a new solid-phase technique (cf. Scheme 7); this favorable separation from the resin also allows both fast isolation of the synthesized fragments for purity checks and the preparation of peptide intermediates whose side chains are still protected. Moreover, a peptide chain that has been removed can be attached again to the polymer. *E. Bayer*[76] and *Merrifield*[77] have offered useful suggestions for the removal of the peptide chain from the polymer with simultaneous amide formation; whereas *Bayer* obtains a suitable resin by attachment of long-chain aliphatic alcohol residues to the phenyl groups of polystyrene[*], *Merrifield* suggests the use of polymeric diphenylmethane as the support material. The removal of the synthesized peptide chain with hydrogen fluoride leads directly to the peptide amide in the latter case (cf. Scheme 7).



Scheme 7. New types of solid supports. (P) = polymer.

Felix and *Merrifield*[17] have recently tried an improvement of the polymer-benzyloxycarbonyl method described by *Letsinger*[16], in which the linkage step is carried out by the azide method using intermediate BOC hydrazides. According to *E. Bayer et al.*, the dependence on "deceptive" diffusion effects is greatly reduced by the use of "pellicular" solids. The authors use glass beads about 100 nm in diameter, coated with a thin film of Merrifield polymer[50], or porous glass beads, quartz spheres, or silica gel with their surface silanol groups covalently bonded to *p*-bis(hydroxymethyl)benzene to form the monoether, so that a benzyl alcohol grouping remains free for the attachment of the first amino acid by formation of the benzyl ester[76,78,79] (cf. Scheme 7). According to the authors, this technique allows a solid-phase synthesis in a column process, and can be automated. As a result of the shorter reaction times due to the fast diffusion of the head components, not only is the yield improved, but the proportion of failure sequences can also be reduced.

Regarding 2: On the basis of progress in the technique of linkage without racemization, *Weygand et al.*[80] have also tried fragment linkage for the solid-phase synthesis. Despite the expected increase in the reaction times, which was in fact observed, this reaction technique was successful; above all, one has always the choice of forming the peptide linkage for which the most favorable reaction is to be expected on the basis of empirical results. The obvious advantage of fragment linkage over step-by-step synthesis is the substantial limitation of the proportion of failure sequences[81].

The "Mukaiyama technique"[82][**] is regarded by *Merrifield*[83] as an advance in linkage technique, though it still involves stepwise synthesis. It remains to be seen whether this method is also suitable for the linking of fragments.

Correction of the first reaction in a conventional stepwise synthesis is nearly always regarded as the avoidance of residual free amino groups. If *Hagenmaier*'s observations[48] are correct, however, it seems that it is not always quantitatively possible even by carefully thought-out acylation reactions *e.g.* with 3-nitrophthalic anhydride[84] or with the intramolecular anhydride of 3-sulfopropionic acid[85]. The amino functions that escape amino-acylation probably owe this largely to the prevailing steric situation. The possibility of nucleophilic opening of acylating reagents from the molecular dimensions of acetic anhydride upward is accordingly limited.

It remains to be seen whether the prospects of success are better with deamination reactions. In this connection, mention should be made of deamination experiments with difluoroamine[86]. This difficult preparative possibility, the technique of which has not yet been fully developed, would certainly overcome the steric problem. The HNF_2 molecule should be small enough to reach any residual free amine function.

Regarding 3: Analytical methods for the fast determination of the percentage reaction (linkage and deacylation step) have not progressed very far, despite various approaches. The use of ^{14}C-labeled BOC-amino acids[***] is too expensive in the long-term view[87]. All other methods make use of "equivalent analysis", which is unsuitable for the solid supports used so far, color reactions[88] with an excessively wide error margin, or chemical reactions that are associated with the same uncertainty as the reaction to be determined (see Section 2.3).

[*] Aminolysis of the ester linkage in liquid ammonia/dimethylformamide.

[**] Formation of the peptide linkage from the components with triphenylphosphane and dipyridyl disulfide.

[***] Obtained in the usual manner from ^{14}C-BOC azide.

4. Conclusion

This critical consideration of the present situation with regard to the synthesis of peptides should end with the following remark. There is little probability that a single "synthesis strategy" will provide a general solution to the problems that face us in the synthesis of natural proteins. The best method will vary with the sequence in question, and it seems quite possible that the best prospects are to be found in a rational combination of various features of the strategies mentioned.

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Bifunctional Reagents for the Crosslinking of Proteins

By Hugo Fasold, Jürgen Klappenberger, Christa Meyer, and Heinz Remold[*]

Proteins can be crosslinked by chemical compounds without any accompanying change in the complicated three-dimensional structure. Many bifunctional reagents that can react with functional groups in the side chains of the amino acids are now known. Not only can the distance between the linked amino acid residues be deduced from the known length of the bridge introduced, but information can also be obtained concerning changes in conformation during other reactions and concerning the arrangement of the components of a quaternary structure.

1. Introduction

The repeated combination of α-amino acids *via* their α-amino and α-carboxyl groups to form peptide linkages leads to the formation of the backbone of a protein molecule, *i. e.* the *main chain* or *peptide chain*. The characteristic residues attached to the α-C atoms of the amino acids branch off from the main chain as side chains. The conformation of the main chains and side chains is evidently determined at the site of the protein biosynthesis by the genetically determined sequence of the amino acids. Interactions between the side chains force the entire molecule into a rigid, three-dimensional structure that is capable only of slight movement in small regions.

The *sequence* of the amino acids is known as the *primary structure*. The conformation of the main chain and all its side chains is called the tertiary structure; characteristic subunits such as helices can be distinguished as a secondary structure (see also Fig. 1). Several main chains are sometimes covalently linked by disulfide bridges to form a tertiary structure (see Fig. 3). If several tertiary structures combine in a little dissociated aggregate, without covalent links between them, to form one molecule, this is referred to as a *quaternary structure*.

In the tertiary structures that have been established so far, most of the hydrophobic side chains are packed tightly together in the interior of the molecule with exclusion of water, while the ionizable and polar side chains are situated on the surface of the molecule in contact with the surrounding water. This second group can undergo chemical substitutions; examples are the acylation of the ε amino group of lysine, the alkylation of the SH group of cysteine, and the nitration of the phenolic side chain of tyrosine with tetranitromethane. *Zahn*[1-3] has suggested the introduction of artificial crosslinks into the protein by carrying out such reactions with bifunctional bridging reagents.

2. Possible Applications

The crosslinking method has so far been proposed for three types of problems:

1. To allow the determination of the distance between two functional groups in a protein molecule, these groups must be linked by a rigid bifunctional reagent. After enzymatic degradation of the crosslinked protein, it is then necessary to identify the partial sequences in the primary structure of the protein to which the two ends of the bridge are attached. Many polar side chains on the protein surface possess a limited mobility; the distance found from the crosslinking reaction is therefore a value lying between upper and lower limits (see Table 1).

2. Some proteins undergo characteristic and physiologically significant changes in conformation. Allosteric enzymes, for example, are rearranged by a low molecular weight product of metabolism with a specific point of attachment on the protein in such a way that their enzymatic activity increases or decreases on attachment of this ligand. One can try to block this change in conformation by crosslinking in order to obtain information about the mechanism of the rearrangement from the position of the bridges introduced. Moreover, some types of crosslink may be formed in only

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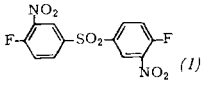
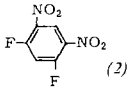
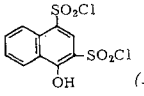
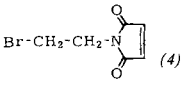
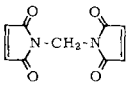
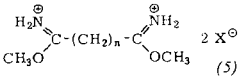
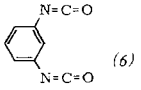
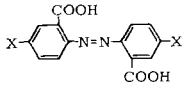
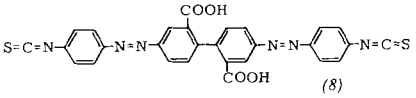
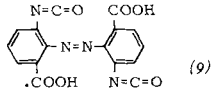
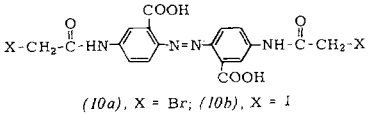
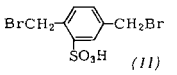
one of the conformers. It is then possible to establish the part of the molecule that is mainly affected by the rearrangement.

3. Crosslinks between two protein molecules should help to establish the positions and the contact areas of the individual proteins in multienzyme complexes, membrane preparations, or other protein aggregates. It is becoming increasingly clear from the investigations on the known enzymes with quaternary structures and on membrane enzymes how strongly the catalytic activity of the subunits of such systems can be regulated by contact with their neighbors.

3. Reagents and Interpretation of the Experiments

Table 1 shows a few members of each class of substances synthesized for the purpose of crosslinking. Azo dye reagents, in addition to their rigid structure, have the advantage that cleavage is possible in a mild reaction with dithionite. After enzymatic degradation of a protein crosslinked with azo dyes, therefore, the two bridgehead peptides can be isolated separately from the azo-peptides. Moreover, a link between two different protein molecules can be broken again without damage to peptide bonds.

Table 1. Reagents for crosslinking in proteins.

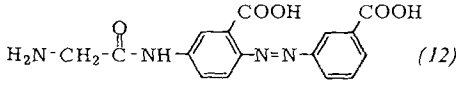
Formula	Side chains linked	Length of link in main chain (Å)	Ref.
 (1)	Lysines (Cysteines, Tyrosines, Histidines)	6—18	[1]
 (2)	Lysines (Cysteines, Tyrosines, Histidines)	3—12	[1]
 (3)	Lysines (Cysteines, Tyrosines, Histidines, Serines)	3—12	[4]
 (4)	Cysteines (Histidines, Lysines)	4—14	[5, 6]
 (4a)	Cysteines (Histidines, Lysines)	4—14	[5, 6]
 (5)	Lysines	dependent on *n*	[7]
 (6)	Lysines (Cysteines, Tyrosines, Serines, Histidines)	4—14	[8]
 (7a), X = N=C=O; (7b), X = N=C=S	Lysines (Cysteines, Tyrosines, Serines, Histidines)	6—24	[9]
 (8)	Lysines (Cysteines, Tyrosines, Serines, Histidines)	16—34	[11]
 (9)	Lysines (Cysteines, Tyrosines, Serines, Histidines)	3—10	[11]
 (10a), X = Br; (10b), X = I	Cysteines (Histidines, Lysines)	6—22	[10]
 (11)	Cysteines (Histidines, Lysines)	4—16	[12]

The first step in the interpretation of crosslinking experiments for the determination of distances is always the detection of the bridges incorporated by the "fingerprint method". The proteins must first be broken down by enzymes that, like trypsin, reproducibly hydrolyze the peptide linkages only at a few points in the sequence. The peptides in the resulting mixture are separated by a two-dimensional combination of high-voltage paper electrophoresis and paper chromatography. A characteristic peptide pattern is thus obtained for any protein. The pattern of the new bridge peptides that appear in the case of crosslinked proteins allows the characterization of the tertiary structure of the protein. The three-dimensional structures of related sequences can thus be compared. An example of the application of this method is given for the digestive enzyme chymotrypsin and its precursor chymotrypsinogen[11].

4. Sources of Error and Interfering Factors

The coupling of the predominantly hydrophobic reagents to the protein may upset the natural folding of the molecules. After crosslinking, therefore, it is necessary to verify that the three-dimensional structure has not been affected, *e.g.* by enzyme-kinetic measurements, determination of the accessibility of various families of side chains to chemical modifications, or measurement of the rotatory dispersion and of the molecular volume[13].

A proportion of the reagent molecules will react by only one of their functional groups with the protein, since the second functional group will not always find a reaction site at a suitable distance. Spurious crosslinks are therefore formed during further treatment. It was necessary in some cases to stop crosslinking *e.g.* with the dye *(12)*.



(12)

Undesirable crosslinking of the bifunctional reagent with two protein molecules to form false dimer molecules can be easily avoided.

5. Examples

5.1. Insulin

The first identification of a crosslink was achieved by *Zahn* in insulin[4]; it was formed by the reagent *(2)* between the N-terminal groups of the two peptide chains of the molecule, which are linked by disulfide bridges. This result was confirmed by the recently completed X-ray structural analysis of insulin crystals. Experiments with the same reagent also led to the first crosslinkage (between an N-terminal group and a lysine side chain) of two protein molecules. This was taken as evidence that the molecules are parallel in the stable aggregates of insulin, which are not dissociated in solution.

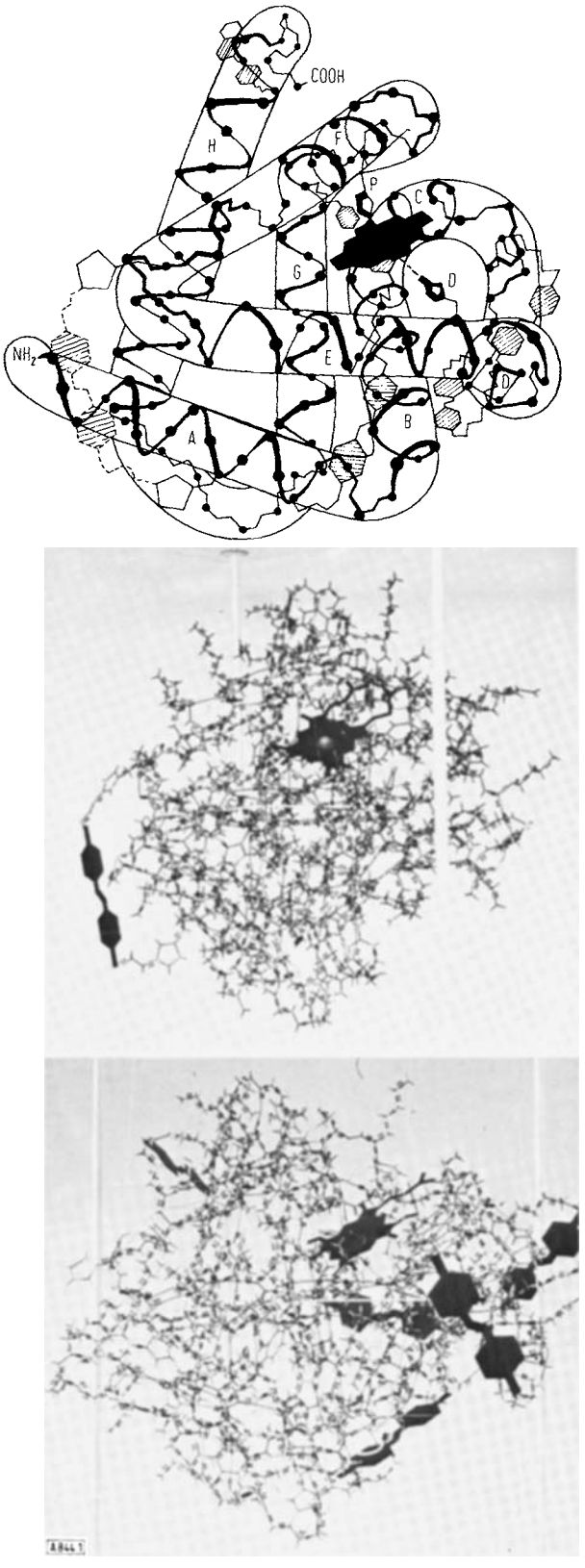


Fig. 1. Top: Conformation of the peptide main chain of whale myoglobin (according to *R. E. Dickerson*). NH_2, COOH: amino and carboxyl ends respectively of the chain. The helical regions of the main chain, which are situated in the linear parts of the structure, are labeled with the letters A, B, C, *etc.* from the amino end. The black area shows the outline of the porphyrin ring. Two histidine side chains (P and D) from the F helix (proximal) and from the E helix (distal) respectively are drawn toward this ring. The oxygen molecule is attached to the iron complex on the same side as the distal histidine. The five crosslinks formed with the reagents *(7a)* and *(7b)* between lysines (continuous lines) and the crosslink formed with the reagent *(10a)* between two histidine side chains (broken line) are shown. Center: Rod model of whale myoglobin with crosslinks inserted between histidine side chains [reagent *(10a)*]. Bottom: Same model with crosslinks between lysine side chains [reagents *(7a)* and *(7b)*].

5.2. Whale Myoglobin

The known tertiary structure of whale myoglobin was used as a subject for the measurement of intramolecular distances with a series of azo dye reagents of the type *(7)—(10)*. The crosslinks found all agreed with possible distances based on the model of the molecule (Fig. 1). Partial denaturation was detected only on introduction of six azo dye bridges per molecule. This was particularly easy to recognize in the heme-containing protein by the change in the absorption spectrum; the accessibility of the imidazole ring of histidine was also measured[11, 13, 14].

5.3. Ribonuclease

In bovine pancreas ribonuclease, which can cleave phosphoric acid diester linkages in ribonucleic acids at pyrimidine bases, two lysine side chains (positions 7 and 41) can be linked by the reagent *(2)*. The change in the enzymatic activity showed that the crosslink must be situated in the immediate vicinity of the active center (Fig. 2)[15].

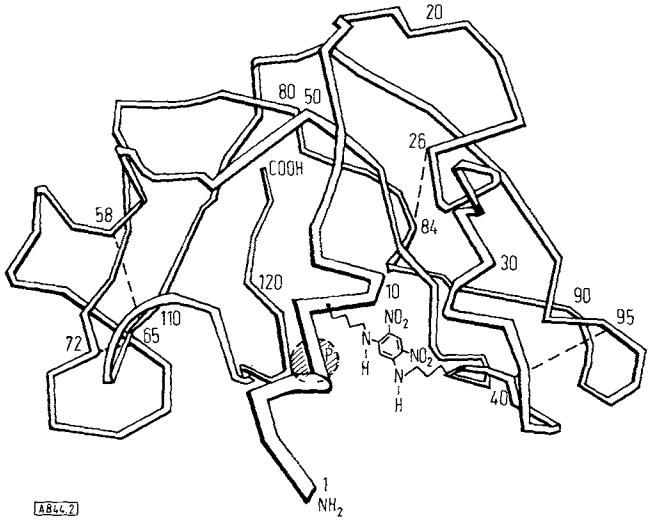


Fig. 2. Conformation of the peptide main chain of bovine pancreas ribonuclease (after [17, 18]). NH_2, COOH: amino and carboxyl ends respectively of the chain. The numbers indicate the positions of the amino acids in the sequence of the molecule. Broken lines: disulfide bridges. P: point of attachment of the substrate to the enzyme molecule. The crosslink formed between two lysine side chains by the reagent *(2)* (positions 7 and 41) is shown (after [15]).

The determination of the peptide sequence in the vicinity of the bridge, together with the results of stepwise blocking experiments on histidine side chains, helped to elucidate the mode of action of the enzyme. It was found that the two imidazole rings of the side chains 12 and 119 are involved together in the essential steps of the catalysis[16]. This hypothesis has been impressively confirmed by the results of the X-ray structural analysis.

5.4. Chymotrypsin and Chymotrypsinogen

The inactive precursor chymotrypsinogen, which is synthesized in the pancreas, loses two dipeptides in the intestine to form the active digestive enzyme chymotrypsin (see Fig. 3). The main chain of the proenzyme is thus broken down into three partial chains, which are linked by disulfide bridges. Two amino acid side chains in the active center of the molecule, *i.e.* histidine in position 57 and serine in position 195, are thus brought into close proximity with each other; the activation of the proenzyme therefore leads to a rearrangement of the tertiary structure. Reproducible fingerprints of the azo bridge peptides were obtained for chymotrypsinogen and chymotrypsin after crosslinking with the reagents *(7a)* and *(7b)*. The fingerprints were almost identical. This led to the conclusion that the rearrangement of the tertiary structure on activation of chymotrypsinogen must affect only a limited part of the folded molecule. The blueprint of the peptide main chain must be almost identical in the two proteins, since any pronounced change would strongly affect the crosslinking pattern. Three of the azopeptides were isolated from crosslinked chymotrypsinogen and identified. These are shown in Figure 3 in the tertiary structure of chymotrypsin, which

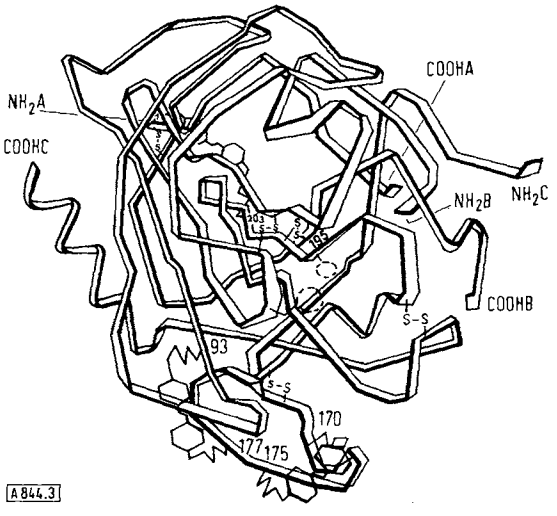


Fig. 3. Conformation of the peptide main chain of bovine pancreas chymotrypsin (after [19]). By elimination of two dipeptides (positions 14—15 and 147—148) from the peptide chain of the inactive precursor chymotrypsinogen on activation in the intestine, the three individual chains A, B, and C, which are linked by disulfide bridges, are formed. NH_2A, COOHC: amino and carboxyl ends respectively of the original peptide main chain of chymotrypsinogen. NH_2B, COOHA: new amino and carboxyl ends formed by elimination of the dipeptide in positions 14—15 of the chymotrypsinogen chain. NH_2C, COOHB: new amino and carboxyl ends formed by elimination of the dipeptide 147—148 from the chymotrypsinogen chain. Dotted circles: schematically indicated locations of the two side chains in the active center, histidine (position 57) and serine (position 195). The three crosslinks identified in chymotrypsinogen with the reagents *(7a)* and *(7b)* are shown (after [11]). —S—S—: natural disulfide bridges. The numbers indicate the positions of the amino acids in the sequence of chymotrypsinogen.

has now been elucidated by X-ray structural analysis[19]. This observation has been confirmed in the meantime by the comparative X-ray structural analysis of chymotrypsinogen.

5.5. Hemoglobin

Several groups of workers have set out to form crosslinks in hemoglobin and to identify their positions. In hemoglobin, four tertiary structures are combined to form a

quaternary structure. The four tertiary structures consist of two identical pairs, which are known as the α and β chains. The X-ray structural analysis carried out by *M. F. Perutz* and co-workers first gave the three-dimensional arrangement of the four chains with respect to one another (see also Fig. 5), and have progressed now to the precise localization of the atoms in this three-dimensional structure[20].

It was recognized at an early date that the quaternary structure changes on combination with or release of oxygen. This rearrangement is the result of the mutual effects of the four chains, which can also be seen in the characteristic oxygen saturation curve of the protein (Fig. 4). In contrast

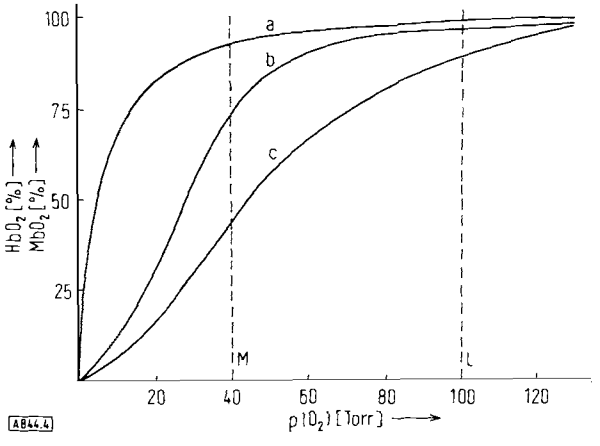


Fig. 4. Course of the oxygen-binding curves of myoglobin (a) and hemoglobin at pH = 7.4 (b) and at pH = 6.8 (c). Broken lines: oxygen partial pressure in the peripheral tissue, *e.g.* in muscle tissue (M), and in the lungs (L).

with the curve of the monomeric heme protein myoglobin, the curve for hemoglobin follows a distinct sigmoid course, since the bonding of the oxygen molecule to one or more subunits increases the affinity of the others for the substrate. This property is necessary for optimum O_2 uptake in the lungs and optimum release of O_2 in the peripheral tissue (Fig. 4). A second characteristic of the interaction is seen in the alkaline Bohr effect: on release of oxygen, the p*K* value of several functional groups increases; in the physiological pH range of blood, the protein takes up 0.8 proton per subunit, which it releases again in the lungs during uptake of oxygen. This buffering action allows the transport of carbon dioxide away from the tissue.

The tertiary structures of myoglobin and of the hemoglobin chains are almost identical. They change only slightly on uptake or release of oxygen. The displacements of individual atoms in the neighborhood of the heme during these processes are less than 1 Å. The rearrangement of the quaternary structure, on the other hand, involves displacements of up to 8 Å.

The oxygen affinity of deoxyhemoglobin, and hence that of the subunits, is less than that of the oxy form. It is not yet certain at what point in the oxygenation of the molecule the affinities, the quaternary structures, and the p*K* values (Bohr effect) change. Until recently, it was also unknown how the mutual interaction at the interfaces between the four subunits arises.

Crosslinking reactions were helpful in finding a hypothesis in this case. Crosslinks firmly fixed in the interior of the tertiary structures should influence the oxygen-binding capacity of the molecule as a whole if they are situated close to a region of the interfaces that is particularly important to the interactions between the subunits. Attempts were made in particular to form bridges between different subunits. The idea was that this should show how the binding of oxygen is affected by hindrance of the change in the quaternary structure. The reagents *(4)*, *(4a)*, and *(10b)* were used, since it was necessary for these to react first with the two SH groups of the cysteines in position 93 of the β chains, which lie on the surface of the molecule. The two reagents derived from maleimide formed crosslinks within the β chains [*(4)* to histidine 97 and *(4a)* to the amino end group of the β chains][6]. In the crosslinking reaction with *(10b)*, it was possible to isolate two hemoglobin derivatives, the structures of which are shown in Figure 5. All these derivatives changed the sigmoid O_2 binding curve to the hyperbolic shape of the curve for monomeric myoglobin, *i.e.* the interactions of the subunits had been eliminated (Fig. 4).

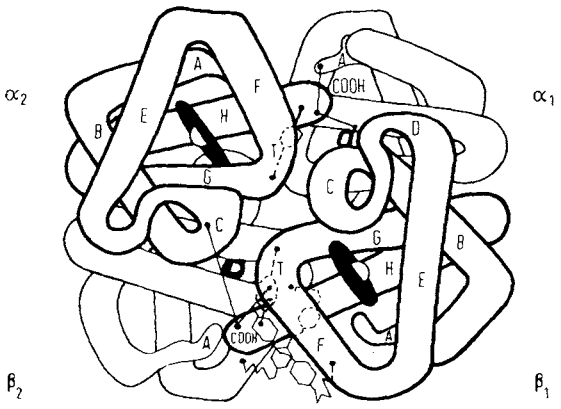
The three crosslinks within the two β chains of the molecule, when fitted into the detailed model of hemoglobin[21], show the same effect on the molecular structure. The carboxyl end groups of the β chains are displaced by several Å from their normal positions.

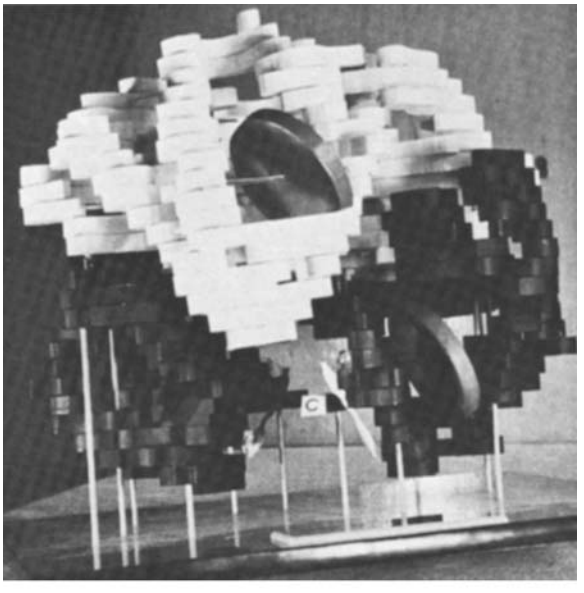
The displacement depended on the covalent bonding of both functional groups of the reagent; the corresponding monofunctional reagents caused only a slight change in the oxygen binding after attachment to cysteine β 93.

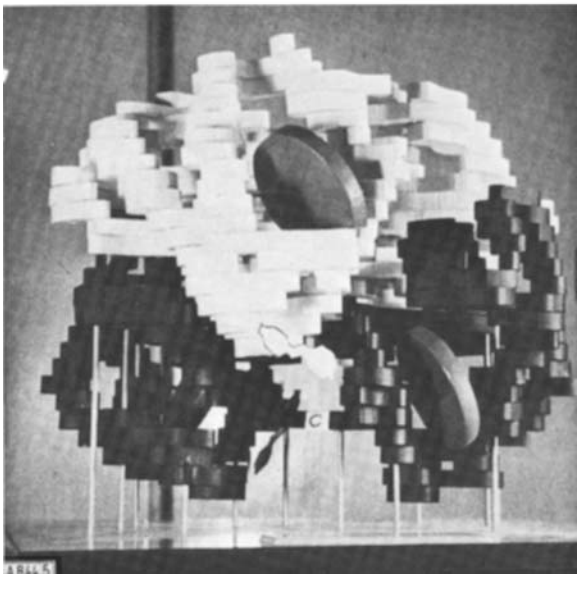
The carboxyl end groups of all four chains are freely mobile in oxyhemoglobin. In deoxyhemoglobin, on the other hand, each of these four amino acids is firmly anchored by two salt bridges (Fig. 5). The carboxyl groups of the arginines in the α chains are linked to the amino end groups of the valines in the opposite α chains, whereas their guanido groups are joined to the carboxyl groups of the aspartic acid in position 126 (helix H) of the opposite α chain. Similarly, the carboxyl groups of the histidines at the ends of the β chains are linked to the ε-amino groups of the lysines in position 40 (helix C) of the neighboring α chain (*e.g.* β_1 with α_2), while the imidazole ring is linked to the carboxyl group of the aspartic acid in position 94 of the same β chain.

Together with this anchoring of the carboxyl end groups on transition from oxyhemoglobin to deoxyhemoglobin, the side chains of the tyrosines in the penultimate positions of all four chains are linked in the interior of the four tertiary structures (see Fig. 5). As a result of the fixation of the carboxyl end groups, they are inserted in recesses between the helices F and H, where they are held partly by van der Waals forces and partly by the hydrogen bonds shown in Figure 5 between their hydroxyl groups and the carbonyl groups of the peptide linkage of valine at the junction between the F and G helices. The tyrosines cannot emerge from these recesses without simultaneous rupture

of the salt bridges of the carboxyl end groups. The crosslinking reactions carried out and characterized in the oxy form with the reagents *(4)*, *(4a)*, and *(10a)* (Fig. 5) in any case prevent the formation of the expected bonds of the carboxyl ends and the tyrosines on transition to the deoxy form, and thus fix the two β chains in the oxy form.







The course of the rearrangement of hemoglobin on oxygen uptake, which was recently published by *M. F. Perutz*[23], is based, among other observations, on the blockage of the transition in typical deoxy structures when the molecule contains crosslinks of this type. The X-ray structural analysis of hemoglobin crystals has shown that on oxygenation of the individual chains, the iron atoms, which project about 0.8 Å from the plane of the porphyrin rings toward the F helices in the deoxy form, are withdrawn into this plane. It is not known how the pull that moves the imidazole group of the histidine from the F helix (see Fig. 1) by at least 0.2 Å toward the porphyrin ring is translated into a change in the tertiary structure in the region of the E, F, and H helices. The two α chains probably first react with oxygen molecules, since they have room both in the oxy form and in the deoxy form for the addition to the sixth coordination site of the iron. In any case, it can be shown that the F helices move slightly toward the H helices, as a result of which the linkage of the tyrosine side chains mentioned apparently becomes impossible. If the bonds in the two α chains are broken, the terminal arginines must also give up their salt bridges. Since these lead to other chains, the quaternary structure is then loosened to such a degree that it can change into the oxy form. At the same time, a proportion of the protons becomes free and causes the Bohr effect. However, the salt bridges between the carboxyl ends of the β chains and the adjacent α subunits are broken by the rearrangement, so that only the two salt bridges within the β chains remain intact. This is evidently enough to facilitate greatly the addition of oxygen with liberation of the carboxyl end, whereupon the remaining "Bohr effect protons" become free. These processes cannot take place in the crosslinked derivatives, since the attachment of the tyrosines and carboxyl end groups on release of oxygen from the two β chains is prevented, and the quaternary structure therefore remains in the oxy form.

The second component crosslinked with the reagent *(10b)* (Fig. 5) has the same crosslinking in a β chain as the symmetrical derivative. The accessible SH group of the other β chain is linked to the imidazole ring of the histidine 46 of the adjacent α chain. It is known from other experiments[24]

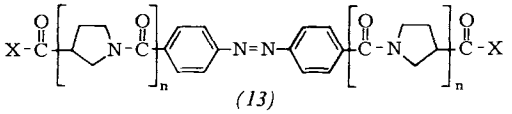
Fig. 5. Top: Conformation of the four peptide main chains of the hemoglobin molecule as in Fig. 1. The letters A—H denote helical regions as indicated in Fig. 1, A being at the amino ends of the individual chains and at the beginning of the A helix. COOH: carboxyl ends of the chains. The black areas with white spheres incorporated denote the porphyrin rings with iron atoms. The two salt bridges of the terminal histidines and arginines at the carboxyl ends of the β_1 and α_2 chains in the foreground are indicated schematically as lines. The incorporation of the side chains of the tyrosines (T) in the penultimate position into the tertiary structure by hydrogen bonds to the peptide linkage in the region of the F—G transition is also shown for these chains (see text). The two crosslinks formed with the reagent *(10b)* within the two β chains are also shown. Center: Hemoglobin models with crosslinks introduced by the reagent *(10b)*. C: carboxyl ends of one of the two β chains (black). The crosslinks within the two β chains run from cysteine in position 93 to lysine in position 82 in the vicinity of the carboxyl end. Bottom: Same model with crosslinking within a β chain (in the background, as in center illustration) and interchain crosslinking of cysteine in position 93 of the β_1 chain to histidine 45 of the neighboring α_2 chain (in the foreground) [22].

that the modification of only one β chain is not enough to block the interaction of the molecule as a whole with oxygen. Since this derivative also exhibits the myoglobin type of oxygen-binding curve, the interchain crosslinking, *i.e.* the fixation of the quaternary structure of the protein according to the model, can hinder the rearrangement from the deoxy form into the oxy form as effectively as the blockage of the terminal histidines of the β chains. The change in the quaternary structure, according to these experiments, is then a necessary condition for the transition between the oxy and deoxy forms of the tertiary structures.

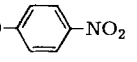
6. Outlook

Apart from the experiments on insulin and hemoglobin mentioned, very few linkages of two tertiary structures or protein molecules with bifunctional reagents have been achieved[25]. Most of the reagents used so far are too short; longer reagents are too hydrophobic, and cause denaturization or unfolding of the protein even on introduction of one to two molecules per tertiary structure.

Reagents having the formula *(13)* were synthesized especially for crosslinking. Oligoproline has the structure of an



(13)

X = Cl, -O- 

elongated, rigid helix beyond $n=5$[26]. The molecule is hydrophilic, and the denaturing effect on proteins is very small. Since the oligoprotein component may be made as long as one wishes, reagents of this kind can be used for the investigation of numerous biological protein associates.

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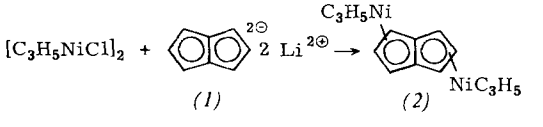
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COMMUNICATIONS

Allyldihydropentalenylene Complexes of Transition Metals

By *Akihisa Miyake* and *Atsuo Kanai*[*]

Reaction of allylnickel chloride with dihydropentalenylenedilithium *(1)*[1] yields diallyldihydropentalenylenedinickel *(2)*[3] as deep green crystals.



(1) *(2)*

Compound *(2)* is stable at room temperature (sintering above 145 °C with decomposition) and is monomeric in benzene. Hydrogenation of *(2)* gives propane and *cis*-bicyclo[3.3.0]octane. The ^{1}H-NMR spectrum (in C_6D_6) exhibits two signals for the dihydropentalenylene protons at $\tau=3.97$ (2 H/t, $J=2.4$ Hz) and 4.81 (4 H/d, $J=2.4$ Hz), as well as three signals for the π-allyl protons at $\tau=5.11$ (2 H/septet, $J=6.0$ Hz), 6.93 (4 H/d, $J=6.0$ Hz), and 8.49 (4 H/d, $J=12.0$ Hz).

X-ray structure analysis[2] showed the molecule to possess a center of symmetry and to have the two nickel atoms *trans* to each other (see Figure; Ni—Ni distance 4.31 Å).

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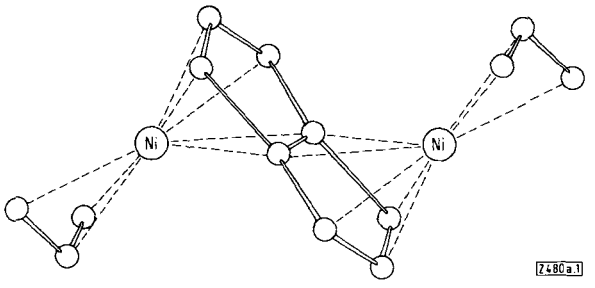


Fig. Structure of diallyldihydropentalenylenedinickel *(2)*.

In similar reactions we have prepared tetraallyldihydropentalenylenedichromium *(3)*[3] as reddish brown crystals which decompose above −20 °C and hexaallyldihydropentalenylenedizirconium[3] as reddish violet crystals which decompose above −10 °C. Compound *(3)* is paramagnetic. The temperature dependence of the ESR signal intensity[4] follows the Curie law, thus indicating that the unpaired electrons of both chromium atoms are mutually independent, *i.e.*, that the chromium atoms in *(3)* are also *trans* to each other.

Diallyldihydropentalenylenedinickel (2):

A solution of *(1)* (3.0 g) in THF (150 ml), which is cooled to −78 °C, is slowly added dropwise to a stirred solution of allylnickel chloride (4.9 g) in THF (100 ml) at −30 to −40 °C. After 16 hours' stirring at −20 °C the THF is evaporated off at room temperature. The residue is extracted with ether (100 ml) and then extracted continuously with a 200-ml volume of ether for 20 h. The extract is diluted with ether, filtered, and evaporated to 250 ml. The deep green crystals that precipitate at −78 °C are recrystallized from ether (600 ml) at −78 °C; yield 2.5 g (46% based on C_3H_5NiCl).

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[3] All the complexes described gave correct elemental analyses.

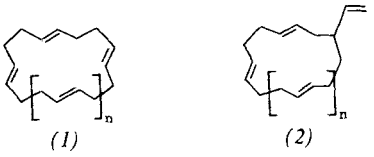
[4] We are grateful to *D. K. Ohigashi* for recording and discussing the ESR spectra.

Catalytic Formation of Macrocyclic Polyenes from Butadiene

By *Akihisa Miyake, Hisao Kondo*, and *Masaki Nishino*[*]

Cyclodimerization[1] and cyclotrimerization[2] of butadiene are known to occur on nickel catalysts. We have found that cyclotetramerization, cyclopentamerization, and cyclohexamerization, as well as higher cyclooligomerization, of butadiene are also possible by using certain nickel catalysts.

Butadiene is converted into a viscous liquid at room temperature in the presence of a catalyst system comprising bis(π-allyl)nickel and π-allylnickel chloride. Apart from cyclic dimers and trimers, the product also contains a high boiling fraction (b. p. 70—260 °C/1 torr) and a waxy residue in a total yield of about 70% (based on reacted butadiene). The high boiling fraction contains cyclopolyenes of structure *(1)*, $n=1$—6, lesser amounts of vinylcyclopolyenes of structure *(2)*, $n=1$—6, and small



(1) *(2)*

amounts of open chain oligomers. All the compounds of type *(1)* and *(2)* could be separated by fractional distillation. Proof of the structure is provided by elemental analysis, molecular weight determination, mass, IR, and NMR spectra, hydrogenation, and ozonolysis. The IR spectra indicate that *(1)* and *(2)* contain only *trans* double bonds. Whereas silver nitrate gives crystalline complexes with all-*trans*-1,5,9,13-cyclohexadecatetraene *(1)*, $n=1$, (m. p. 167—169 °C), and all-*trans*-1,5,9,13,17,21-cyclotetracosahexaene *(1)*, $n=3$, (m. p. 141—143 °C), all-*trans*-1,5,9,13,17-cycloeicosapentaene *(1)*, $n=2$, forms only an oily complex.—IR and NMR spectra of the waxy residue closely resemble those of the high boiling fraction. It is undoubtedly a mixture of higher cyclic oligomers or polymers (Tables 1 and 2).

It is an established fact that bis(π-allyl)nickel catalyzes the cyclotrimerization of butadiene[3] and π-allylnickel chloride the 1,4-polymerization of butadiene[4]. The specific activity of our catalyst must therefore be due to interaction of the two components. We assume that the growth of the butadiene oligomer chain takes place on the associated system

Table 1. Properties of the cyclooligomers of type *(1)* and *(2)*. IR spectrum: *(1)*: 960 cm^{-1}; *(2)*: 990, 960, 910 cm^{-1}.

Cpd.		B. p. (°C/1 torr)	n_D^{20}	NMR (τ)
(1),	$n=1$	≈97 [a]	1.5057	4.66 (8H), 7.94 (16H)
(1),	$n=2$	≈142	1.5133	4.70 (10H), 7.96 (20H)
(1),	$n=3$	≈176	1.5133	4.69 (12H), 7.97 (24H)
(2),	$n=2$	≈136	1.5093	4.70 (8H), 5.02 (1H), 5.15 (2H), 7.28 (1H), 7.97 (16H), 8.63 (2H)
(2),	$n=3$	≈170	1.5098	4.68 (10H), 5.02 (1H), 5.14 (2H), 7.30 (1H), 7.97 (20H), 8.60 (2H)

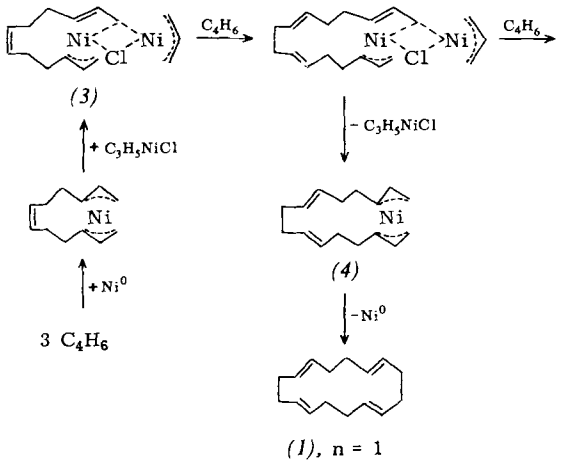
[a] m. p. 19—20 °C.

Table 2. Composition of the reaction product (determined by gas chromatography).

Oligomer	Yield (%) [a]	Composition of oligomer (%)		
		(1)	*(2)*	linear
C_8	4.8	74	26	—
C_{12}	23.2	100 [b]	—	—
C_{16}	4.5	69	4	27 [c]
C_{20}	12.2	85	12	3
C_{24}	11.2	70	26	4
C_{28}	5.4	73	22	5
C_{32}	2.7	72	23	5
$>C_{32}$	36.1			

[a] Based on reacted butadiene.
[b] 85% *trans,trans,trans-*, 12% *trans,trans,cis-*, and 3% *trans,cis,cis*-cyclododecatriene.
[c] Cyclic tetramers of unknown structure are included here.

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(1), n = 1

(3) and that ring closure occurs on the dissociated "naked" nickel as in *(4)*. Accordingly, π-allylnickel chloride should be replaceable by other Lewis acids; experiments designed to test whether this is the case are currently in progress.

Procedure:

A solution of bis(π-allyl)nickel (0.85 g) and π-allylnickel chloride (0.57 g) in toluene (20 ml) is added to liquid butadiene (125 g) in a glass autoclave. The deep red reaction mixture is stirred magnetically for 85 h at room temperature. Unreacted butadiene is blown off. Acetone is added to the residue in the presence of air, precipitated polymer is separated off, and the filtrate is distilled (see Table 2). 58.2% of the butadiene reacted. Conversions of more than 90% without significant changes in the products can be achieved with prolonged reaction times.

This synthesis of *(1)* can be conducted on any scale. The molar ratio of the two catalyst components is not critical. No significant change in activity is recorded for a molar ratio of Ni:NiCl ranging between 0.7:0.3 and 0.4:0.6. A readily accessible system composed of nickel pentanedionate, triethylaluminum, and allyl chloride can also be used instead of bis(π-allyl)nickel and π-allylnickel chloride.

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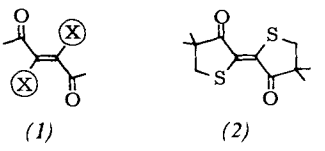
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4,4,4′,4′-Tetramethyl-$\Delta^{2,2'}$-bipyrrolidine-3,3′-dione, a Compound having the Basic Chromophore System of Indigo[1]

By *Eike Wille* and *Wolfgang Lüttke*[*]

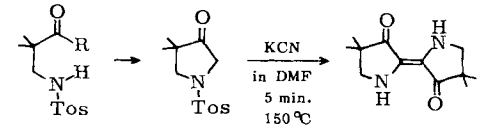
HMO and PPP calculations[2-4] have indicated that the grouping *(1)* is to be regarded as the basic chromophore of indigo. Preparation of compound *(2)* with X=S in grouping *(1)* provided experimental support for the correctness of the theoretical considerations[6, 7]. In order to make a direct comparison with indigo, however, it was necessary to synthesize a compound whose electron donor and acceptor groups resembled those of indigo in nature, configuration, and conformation [*(1)* with X=NH].



(1) *(2)*

We have now accomplished this aim by the synthesis of 4,4,4′,4′-tetramethyl-$\Delta^{2,2'}$-bipyrrolidine-3,3′-dione *(7)* in the following manner:

N-Tosylaminopivalic acid *(3)*, prepared from the alkaline-hydrolysis product of ethyl aminopivalate[8], was converted into the acid chloride *(4)* and thence, by reaction with diazomethane, into the diazo ketone *(5)*. Acidolytic decomposition of the diazo ketone *(5)* in glacial acetic acid gave *N*-tosyl-4,4-dimethylpyrrolidin-3-one *(6)* which yielded the desired product *(7)* (m.p. 159°C) on reaction with potassium cyanide in dimethylformamide.



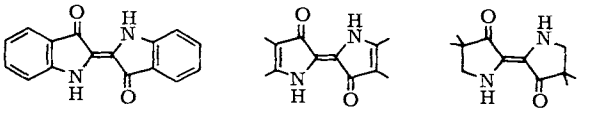
(3), R = OH
(4), R = Cl
(5), R = $CH{=}N_2$

(6) KCN, in DMF, 5 min., 150°C (53%) *(7)*

The structure of *(7)* is established by satisfactory elemental analyses and spectroscopic data: IR (KBr): $\tilde{\nu}$(NH) = 3377, $\tilde{\nu}$(C=O) = 1665; IR (C_2Cl_4): $\tilde{\nu}$(NH) = 3395, $\tilde{\nu}$(C=O) = 1674 cm^{-1}. UV/visible (cyclohexane): λ_{max} = 473 nm (log ε = 4.05), 204 (3.98); (benzene): 483 (4.05); (solid in KBr): 488. NMR ($CDCl_3$): τ = 8.81 (12 H/s, 4 CH_3), 6.63 (4 H/s, 2 N—CH_2), 4.45 (about 2 H/s, 2 NH). Mass spectrum: (*m/e*) 222 (100%) and 207 (42%).

The appearance of *only one* $\tilde{\nu}_{as}$(C=O) and *no* $\tilde{\nu}$(C=C) band indicates that only the *trans* configuration of *(7)* is present.

With the synthesis of *(7)* and the preparation of *(8)* recently reported by *Bauer*[9] there now exists the complete series from indigo *(9)* to the basic chromophore *(7)* with



(9) *(8)* *(7)*

NH as electron donor group. It should therefore prove possible to test the theoretical concept[2-4] of the nature of the basic chromophore system of indigo dyes, which has been the subject of much discussion.

The following points can be deduced from the data presented in Tables 1 and 2:

1. Compound *(7)* exhibits not only the long-wave light absorption but also the gradation of λ_{max} along the series *(9)* → *(8)* → *(7)* required by theory.

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Table 1. Comparison of the measured spectroscopic data with those calculated by the PPP method [4] for indigo *(9)*, tetramethylpyrroleindigo *(8)*, and 4,4,4',4'-tetramethyl-$\Delta^{2,2'}$-bipyrrolidine-3,3'-dione *(7)* [14].

	Compound *(9)*	*(8)*	*(7)*	
λ_{max} (nm)	605	529	487	soln. in tetra-
(log ε)	(4.30)	(3.83)	(4.00)	chloroethane
of the longest	539	483	449	as vapor [10]
wave absorption band	521	502	463	PPP data
oscillator strength f	0.797	0.583	0.465	
$\tilde{\nu}$(C=O) (cm^{-1})	1626	1630	1665	solid in KBr
	1643 [a]	[b]	1670	soln. in C_2Cl_4
	1662	[b]	[b]	as vapor [5]
π bond order	0.752	0.735	0.808	PPP data
$\tilde{\nu}$(NH) (cm^{-1})	3268	3250	3377	solid in KBr
	3405 [a]	[b]	3395	soln. in C_2Cl_4
	3405	[b]	[b]	as vapor [13]

[a] For 5,5'- or 6,6'-dialkylindigo [11].
[b] Not determined.

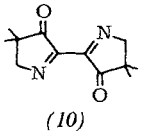
Table 2. Characteristic π-bond orders p(C=O), p(C=C) and charge densities $q(O)_{C=O}$, $q(C)_{C=O}$, q(N) calculated by the PPP method.

	Ground state			First excited state		
	(9)	*(8)*	*(7)*	*(9)*	*(8)*	*(7)*
p(C=O)	0.752	0.735	0.808	0.671	0.667	0.659
p(C=C) central	0.683	0.692	0.668	0.477	0.497	0.437
$q(O)_{C=O}$	1.496	1.502	1.473	1.538	1.503	1.565
$q(C)_{C=O}$	0.740	0.756	0.700	0.843	0.852	0.914
q(N)	1.629	1.605	1.777	1.497	1.491	1.567

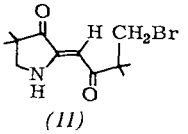
2. The $\tilde{\nu}$(C=O) frequencies observed for *(9)*, *(8)*, and *(7)* are in good agreement with the calculated carbonyl bond orders.

3. The $\tilde{\nu}$(NH) band of *(7)* as a solid is about 100 cm^{-1} higher than the $\tilde{\nu}$(NH) bands of *(8)* and *(9)*; moreover, the $\tilde{\nu}$(NH) frequency of *(7)* increases only slightly (by 18 cm^{-1}) on transition to C_2Cl_4 solution whereas the $\tilde{\nu}$(NH) frequency of *(9)* increases by 137 cm^{-1}. The $\tilde{\nu}$(C=O) band behaves analogously. This would indicate that the molecules of *(8)* and *(9)*, but not those of *(7)*, are connected *via* intermolecular hydrogen bonds in the crystals. The ready sublimation [above 100 °C in high vacuum as against 220 °C for *(9)* and *(8)*] and solubility of *(7)* in polar solvents stem from the same cause.

4. The ease of oxidation of *(7)* is remarkable: The dehydro compound *(10)* was isolated from a benzene solution of *(7)* that had been exposed to atmospheric oxygen for 12 h.



(10)



(11)

A correct elemental analysis and spectroscopic data prove the structure of *(10)* (m.p. 118—119 °C): NMR ($CDCl_3$): τ = 8.78 (12 H/s, 4 CH_3), 5.63 (4 H/s, 2 N—CH_2). IR (KBr): 1742 ($\tilde{\nu}$(C=O)), in C_2Cl_4 1750 cm^{-1}. UV/visible (cyclohexane): λ_{max} = 387 nm (log ε = 2.37), 252.5 (2.91), 215 (3.79).

As a further characteristic of indigo, $\tilde{\nu}$(C=O) and the light absorption of *(7)* (1665 cm^{-1}, 487 nm) and of *(10)* (1750 cm^{-1}, 387 nm) show a gradation which is analogous to that observed for the redox pair indigo *(9)* (1626 cm^{-1}, 605 nm)—dehydroindigo (1736 cm^{-1}, 443 nm).

Reduction of *(7)* leads to a mixture of colorless products.

5. According to the PPP calculations, the charge density on the nitrogen atom of *(7)* is greater than in the compounds *(8)* and *(9)*. The resulting enhanced basicity can actually be observed: In formic acid compound *(7)* is completely monoprotonated at the nitrogen [λ_{max} = 366 nm (log ε = 4.07)], in propionic acid the free and monoprotonated forms of *(7)* can both be detected [λ_{max} = 460 nm (log ε = 2.89) and 368 nm (log ε = 3.94)]. Even in aqueous tartrate buffer of pH 5.4 only a vanishingly small proportion of the neutral form is present [λ_{max} = 368 nm (log ε = 4.03) and $\approx$ 470 nm (log $\varepsilon \approx$ 2.3)]. *N*-Protonation can be deduced from a comparison of the longest wave absorption of *(7)* in acid solution with that of 4,4-dimethyl-2-(4-bromo-3,3-dimethyl-*n*-butan-2-on-1-ylidene)pyrrolidin-3-one *(11)* (prepared by *Fitjer*[12]) whose chromophore structure resembles *(1)* except for a missing amino group [λ_{max} = 365 nm (log ε = 4.09) in ethanol].—Unlike *(7)*, compound *(2)* exhibits a bathochromic shift of the longest wave absorption maximum on addition of acids; however, this effect is observable only with very strong acids.

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[14] We are grateful to Dipl.-Chem. *G. Kunz* for the absorption data of compounds *(7)* to *(9)* in the vapor state and of compounds *(8)* and *(9)* in tetrachloroethane solution. We also wish to thank Dr. *H. Bauer* for kindly supplying us with a sample of compound *(8)*.

Novel Photoalkylation Reactions on the Flavin Nucleus

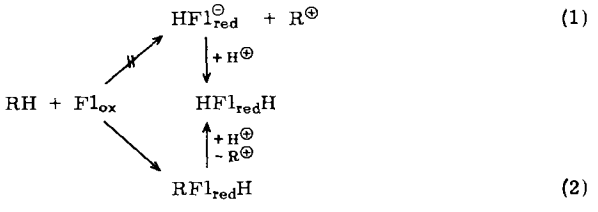
By *Martin Brüstlein*, *W.-R. Knappe*, and *Peter Hemmerich*[*]

Flavin(Vitamin B_2) dependent hydrogen transfer has remained up to the present day as one of those biological reactions for which no formulation in terms of molecular structure has been found. *Wallenfels* and *Gellrich*[1] and

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Suelter and *Metzler*[2] were the first to observe that the flavin-dependent activation of C—H bonds in dihydro nicotinamides is not a radical reaction despite the known stability of flavosemiquinone. In agreement with this, radicals of C—H activating flavoproteins can only be generated artificially, *e.g.* with dithionite, and not by reduction with natural substrates[3].

On the basis of these findings the mechanism of the reaction has been considered as a direct "hydride-transfer" in accordance with Eq. (1). We would suggest, however, that the reaction involves a "group transfer" in accordance with Eq. (2) followed by a protolytic elimination of the residue R^+, the ease of which depends on the nature of R^+.



The following reactions suggest the second of these two possibilities as being the more likely one:

The flavin dependent photodehydrogenation of the cycloolefins given in Fig. 1 in acetonitrile with large excess of substrate proceeds in the order of a few seconds (for experi-

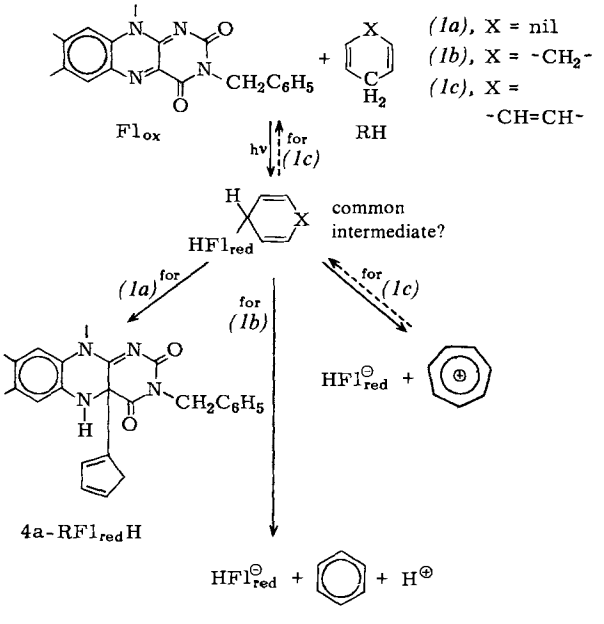


Fig. 1. Photodehydrogenation of cyclopentadiene *(1a)*, 1,4-cyclohexadiene *(1b)*, and cycloheptatriene *(1c)* with 3-benzyllumiflavin in acetonitrile in the absence of oxygen ($\lambda = 445$ nm, bandwidth 16 nm).

mental conditions see Table 1). The reaction course and nature of products depend on the properties of the leaving group R^+.

In the case of the cyclopentadiene *(1a)* a quantitative yield of 4a-(1-cyclopentadienyl)-4a,5-dihydrolumiflavin (4a-$RFl_{red}H$) is obtained. Decomposition of the molecule is energetically unfavorable since the leaving group $R^+ = C_5H_5^+$ is antiaromatic. In fact a decomposition of this covalent "flavin-substrate complex" is only possible by prolonged exposure to a strong oxidizing agent (NO^+).

Table 1. Anaerobic photoreaction of flavin with organic sulfides (acetonitrile, 0.73×10^{-4} mol/l 3-benzyllumiflavin, 0.067 mol/l sulfide, under argon. 250 W/24 V tungsten-halogen lamp with 300—800 nm transparent filter- and lens system).

Substrate	$t_{1/2}$ (s)	Reversibility [%] [a] [b]	[c]	[d]	Main product (λ_{max})
Dimethyl sulfide	150	5	10	76	Adduct (340 nm)
Diethyl sulfide	180	70	81	100	1,5-Dihydroflavin
Methyl *tert*-butyl sulfide	60	21	28	75	Adduct (340 nm)
Ethyl *tert*-butyl sulfide	110	35	75	100	1,5-Dihydroflavin
Methyl phenyl sulfide	55	41	67	83	Adduct (343 nm)
Ethyl phenyl sulfide	120	60	100	—	1,5-Dihydroflavin
Thiolane	50	15	26	88	Adduct (335 nm)
Thiane	110	42	70	93	1,5-Dihydroflavin

[a] Quoted as reoxidation [%] on treatment with the oxidizing agents in [b]—[d].
[b] 1 min air in the dark.
[c] 10 min air in the dark.
[d] 1 min boiling with 50% aqueous acetic acid and sodium nitrite.

Reaction of the flavin with 1,4-cyclohexadiene *(1b)* is completely different: here, no stable intermediate $RFl_{red}H$ can be detected since it decomposes spontaneously and irreversibly to benzene and free dihydroflavin. Cycloheptatriene *(1c)* also behaves in a characteristically different fashion: similarly, no intermediate $RFl_{red}H$ can be observed since the leaving group R^+ (= tropylium ion) is resonance stabilized and only slow secondary decomposition reactions occur. Consequently, in this case the photoreduction of the flavin is reversed in the dark from an initial 12% to a final 3% (Fig. 2). This back reaction can be considered as a recombination of dihydroflavin anion $HFl^{\ominus}_{red}$ and tropylium ion, followed by liberation of the starting substrate cycloheptatriene. The occurrence of this back reaction is confirmed by the fact that 1,5-dihydrolumiflavin $HFl_{red}H$ [generated photochemically as given for *(1b)* in Fig. 1] is reoxidized anaerobically to flavoquinone Fl_{ox} by addition of tropylium bromide. The question as to whether the back reaction leads, at least in part—in analogy to the electrochemical reduction of the tropylium ion[4]—to formation of bitropyl has not been investigated.

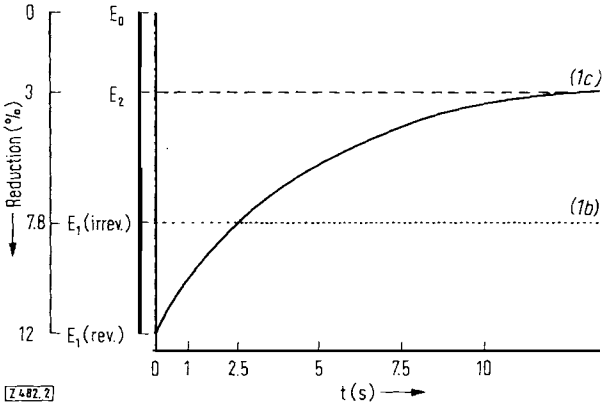


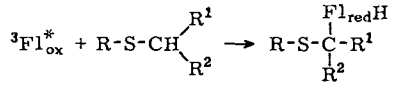
Fig. 2. Photoreaction between 1,4-cyclohexadiene *(1b)* or cycloheptatriene *(1c)* and 3-benzyllumiflavin under anaerobic conditions with subsequent reversing dark reaction in the case of *(1c)*. For experimental conditions see Table 1. The extinction (E) serves as a measure of the reduction of 3-benzyllumiflavin.

The residues R in $RFl_{red}H$ can be fixed, like the C_5H_5-$Fl_{red}H$ described above and like the adduct C_4H_7S-$Fl_{red}H$ *(2)*, previously prepared by us[5], to C-4a or to N-5 of the flavin

nucleus. When R = benzyl, even a mixture of both isomers occurs[6], the 5-$RFl_{red}H$ being rearranged thermally into 4a-$RFl_{red}H$[6].

This rearrangement can be reversed by light in the presence of oxidized flavin as sensitizer[7]. However, it is very difficult to decide whether the migration of such a residue R in the flavin nucleus takes place in the dihydro state or in the radical state[8]. A general tendency for the adduct $RFl_{red}H$ to undergo homolytic cleavage into $R^{\cdot}$ and $\dot{F}lH$ can, however, be ruled out.

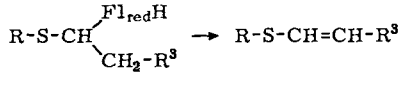
It follows from Table 1 that organic sulfides are dehydrogenated by triplet flavin ($^3Fl^*_{ox}$) in the α-position with formation of an adduct in accordance with Eq. (3).



(3)

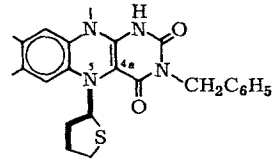
The stability of this adduct depends on the nature and spatial configuration of the leaving group, $R^1R^2CH^+$:

When $R^1 = R^2 = H$, the adduct does not decompose in the absence of oxygen and does so only slowly in its presence. If, however, R^1 = alkyl and R^2 = H or alkyl, then decomposition by elimination [Eq. (4)] is possible and preferred with anaerobic liberation of unsubstituted dihydroflavin that reacts very rapidly with oxygen.



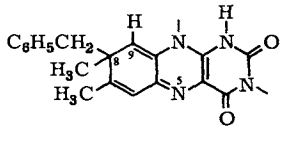
(4)

This elimination is subject to strict steric requirements: The groups to be eliminated must be conformationally in the *anti*-position, and not in an eclipsed or even skewed position to each other[9]. Hence, the ethyl sulfides and thiane (Table 1) react "reversibly", while thiolane forms a stable adduct *(2)* since in this case a *trans* elimination is not possible.



C_4H_7S-$Fl_{red}H$ *(2)*

Further, we presume that the "flavin-dependent C—H activation" under discussion does not—or in any case does not always—lead directly to an adduct bound *via* N-5 or C-4a. In the case of the flavin dependent photodecarboxylation of phenylacetate we can prove this:



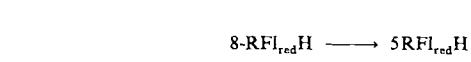
(3)

As mentioned in an earlier report[10], in neutral to alkaline solution a primary product is formed the structure of which we suggest in formula *(3)* on the basis of the following findings:

1. In the ^{1}H-NMR spectrum the methyl group on C-8 of the flavin appears in the region of the aliphatic methyl groups ($\delta = 1.05$ ppm). This assignment is substantiated by comparison with the analogous 8-CD_3 derivative[11].

2. When the reaction is carried out in deuterium oxide, a selective (partial) exchange of hydrogen on C-9 is observed, as is required for a 7-alkylidene-7,8-dihydropteridin[12].

3. Structure *(3)* is also in accord with previously reported absorption spectra [λ_{max} ($CHCl_3$) = 332, 333, and ≈460 nm, longwave end absorption up to 600 nm] and the acid- and heat-catalyzed rearrangement[13]



as a cyclohexadienone-phenol rearrangement[14]; furthermore, it could explain the observation of red, diamagnetic flavin-substrate complexes in flavoproteins[15].

4. Structure *(3)* explains the "action p*K*" of the order of 5 (which is characteristic for the flavin photoreduction and which could not previously be assigned[16]) as deprotonation on N-1. With these results, we hope to make some progress towards a (stereo)chemical understanding of flavin-dependent biological dehydrogenations.

For discussions, suggestions, and communication of data we are indebted to Dr. *G. Blankenhorn* and Dipl.-Chem. *W. Haas*, Konstanz, Dr. *V. Massey*, University of Michigan, and Drs. *G. Radda* and *J. A. T. Taylor*, University of Oxford.

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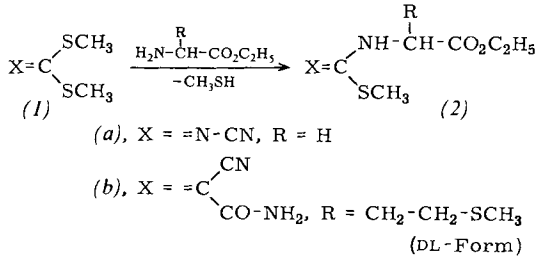
[15] *V. Massey* and *C. Veeger*, Biochim. Biophys. Acta *48*, 33 (1961); *V. Massey* and *Q. H. Gibson*, Fed. Proc. *23*, 18 (1964); *V. Massey* and *B. Curti*, J. Biol. Chem. *242*, 1259 (1967); *V. Massey, R. G. Matthews, G. P. Foust, L. G. Howell, C. H. Williams jr., G. Zanetti*, and *S. Ronchi*, in *H. Sund:* Pyridine Nucleotide-Dependent Dehydrogenases. Springer, Berlin 1970, p. 393.

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New Amino Acid Derivatives from Cyanamide and Cyanacetamide

By *Joachim Gante* and *Günther Mohr*[*]

Six to eight hours' refluxing of dimethyl cyanimidodithiocarbonate *(1a)*[1] and dimethyl (α-cyanocarbamoylmethylene)dithiocarbonate *(1b)*[2] with glycine ethyl ester or DL-methionine ethyl ester hydrochloride, respectively, and sodium ethoxide (molar ratio 1:1:1) in anhydrous ethanol afforded the hitherto unknown amino acid derivatives *(2a)* (yield 50%, m.p. 98—99 °C) and *(2b)* (yield 91%, oil).



(1) *(2)*

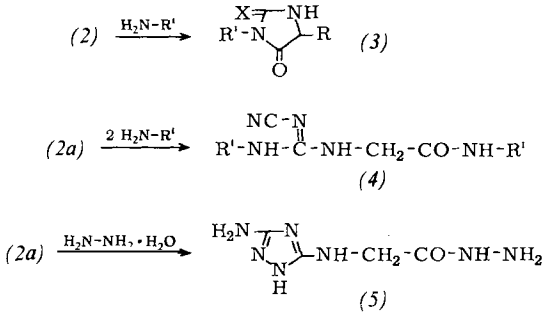
(a), X = =N-CN, R = H

(b), X = =C(CN)-CO-NH$_2$, R = CH$_2$-CH$_2$-SCH$_3$ (DL-Form)

On refluxing for several hours with equimolar amounts of primary amines in ethanol or with an excess of concentrated ammonia/ethanol (2:1), *(2a)* and *(2b)* were converted into the respective hydantoin analogs *(3)* (see Table).

Cpd.	R	R'	X	Yield (%)	M.p. (°C)
(3a$_1$)	H	CH$_2$—CH(CH$_3$)$_2$	=N—CN	28	244–247
(3a$_2$)	H	(CH$_2$)$_5$—CH$_3$	=N—CN	32	168–170
(3a$_3$)	H	CH$_2$—CH$_2$—OH	=N—CN	38	195–196
(3a$_4$)	H	CH$_2$—C$_6$H$_5$	=N—CN	47	239
(3a$_5$)	H	CH$_2$—CH$_2$—C$_6$H$_5$	=N—CN	40	243–245
(3a$_6$)	H	cyclo-C$_6$H$_{11}$	=N—CN	20	229–230
(3b$_1$)	CH$_2$—CH$_2$—SCH$_3$	H	=C(CN)CONH$_2$	46	290
(3b$_2$)	CH$_2$—CH$_2$—SCH$_3$	CH$_3$	=C(CN)CONH$_2$	71	171–172
(4a$_1$)		CH$_3$		93	165–167
(4a$_2$)		CH(CH$_3$)$_2$		60	128–131
(4a$_3$)		(CH$_2$)$_7$—CH$_3$		31	155
(4a$_4$)		CH$_2$—C$_6$H$_5$		82	210

Reaction of *(2a)* with a two- to four-fold excess of amine under otherwise identical conditions gave the urea analogs *(4)*.



(2) *(3)*

(2a) *(4)*

(2a) *(5)*

(2a) and hydrazine hydrate (molar ratio 1:1.8; 2 hours' refluxing in ethanol) furnished *N*-(5-amino-1,2,4-triazol-3-yl)glycine hydrazide *(5)* (yield 79%, m.p. 227—228 °C).

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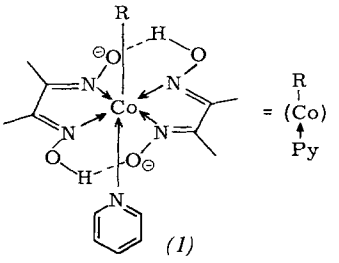
[*] Priv.-Doz. Dr. J. Gante and Dr. G. Mohr
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61 Darmstadt, Frankfurter Strasse 250 (Germany)

[1] *R. J. Timmons* and *L. S. Wittenbrook*, J. Org. Chem. *32*, 1566 (1967).
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Novel Degradation Reactions of Halomethyl Derivatives of Bis(diacetyldioximato)cobalt[**]

By *Gerhard N. Schrauzer*, *Anthony Ribeiro*, *Lian P. Lee*, and *Raymond K. Y. Ho*[*]

Unsubstituted alkylcobaloximes[1] *(1)* with, *e.g.*, R = CH$_3$, which are of interest as model compounds of organocobalt derivatives of vitamin B$_{12}$, generally exhibit a high resistance to attack by alkali. In contrast, studies on halomethyl-

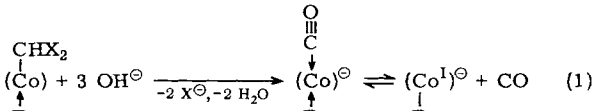


(1)

(1a), R = CHX$_2$ (X=Cl, Br, I)
(1b), R = CH$_2$X (X=Cl, Br, I)
(1c), R = CX$_3$ (X=Cl, Br, I)
(1d), R = CF$_3$
(1e), R = CH$_2$OCH$_3$
(1f), R = COOCH$_3$

cobaloximes *(1a)*—*(1c)* revealed evidence for a surprisingly high alkali sensitivity. Nucleophilic attack of the cobalt-bonded halomethyl group by OH$^\ominus$ ion causes initial Co—C bond cleavage to give halomethanols and cobaloxime(I). The interesting reactions that ensue are reported in the present communication.

In 0.1 N NaOH dihalomethylcobaloximes *(1a)*[2] undergo rapid, quantitative decomposition (no isolable intermediate) into carbonylcobaloxime(I), the carbon monoxide complex of cobaloxime(I), which is at equilibrium with free CO and cobaloxime(I) [eq. (1)].



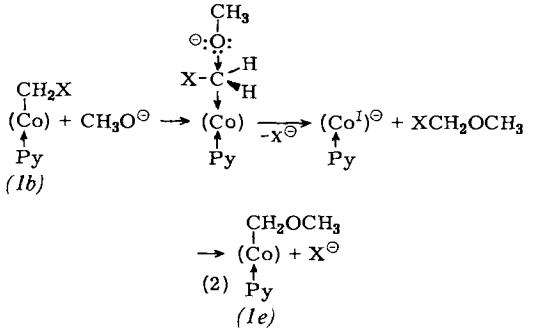
(1a) (1)

[*] Prof. Dr. G. N. Schrauzer, Dr. A. Ribeiro, Dr. L. P. Lee, and Dr. R. K. Y. Ho
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[**] This work was supported by the US Department of Health, Education and Welfare, Grant 1-RO 1 ES 00325-01.

In principle, equation (1) corresponds to a conversion of trihalomethanes into carbon monoxide catalyzed by the nucleophilic cobaloxime(I) since dihalomethylcobaloximes *(1a)* can be prepared from cobaloxime(I) and trihalomethanes[2].

Monohalomethylcobaloximes *(1b)*[2] are cleaved by $NaOCH_3$ in anhydrous CH_3OH with intermediate formation of cobaloxime(I) and halomethyl methyl ethers. Subsequent reaction of the products in absence of air gives methoxymethylcobaloxime *(1e)* which was isolated in 40% yield. The Co—C bond in *(1b)* is ruptured in this case by nucleophilic attack of $CH_3O^{\ominus}$ ion [eq. (2)]:



(1b)

(2)

(1e)

Decomposition of *(1b)* by aqueous alkali also proceeds initially as shown in eq. (2). The resulting halomethanol reacts with the cobaloxime(I), but it proved impossible to isolate hydroxymethylcobaloxime. Instead a complicated series of reactions ensues giving rise to cobaloxime(III) and methane, as well as to traces of methanol and formaldehyde as the final products.

Trihalomethylcobaloximes[4] *(1c)*, and *(1d)* too, also undergo degradation with Co—C bond cleavage on treatment with alkali. Heating of *(1d)* in 2 N NaOH furnishes cobaloxim(I), carbonate and fluoride ion. The complexes *(1c)* are by far the most alkali-labile. Treatment of *(1c)*, X = Cl, with $NaOCH_3$ in anhydrous CH_3OH gives methoxycarbonylcobaloxime *(1f)* in 23% yield.

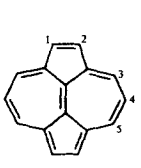
The halomethyl derivatives of vitamin B_{12}[5] are generally more alkali-stable than the corresponding derivatives of cobaloximes; however, they also decompose with Co—C bond cleavage on heating in 1 N NaOH. The reactions observed are possible prototypes for detoxification processes involving the dehalogenation of halohydrocarbons with biogenic metal complexes as catalysts.

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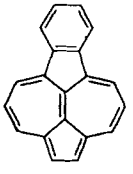
Simple Synthesis of Pyraceheptylene and Benzo[*a*]pyraceheptylene[**]

By *Christian Jutz* and *Erich Schweiger*[*]

Of the three nonbenzenoid (nonalternant) pyrene isomers made up only of five- and seven-membered rings and exhibiting an "aromatic" $4n+2$ Hückel perimeter—pentaleno[2.1.6-*def*]heptalene[1] ($R_E = 5.9495\ \beta$), dipleiapentalene ($R_E = 6.0297\ \beta$), and pyraceheptylene *(1)* ($R_E = 6.0515\ \beta$)—compound *(1)* appears, according to simple HMO calculations[2], to have the greatest resonance energy (R_E). R_E for pyrene is 6.5055 β.



(1)



(2)

A brief account of the preparation of *(1)* has been given by *Anderson*[3]. We have now been able to prepare *(1)* and *(2)* after the manner of a Ziegler-Hafner azulene synthesis[4].

If equimolar amounts of the pentamethine salt *(3)*[5] and the 6-dimethylaminovinylfulvene *(4)*[6] are refluxed together under N_2 for 24 h in pyridine after addition of $NaOCH_3$, the pyridine distilled off in a stream of N_2, and heating to 230 °C in quinoline continued until liberation of dimethylamine ceases, the residue left when the quinoline is distilled off *in vacuo* yields pure pyraceheptylene *(1)* in 5% yield on chromatography, first in methylene chloride and then in hexane, on Al_2O_3 (activity grade III, neutral). Compound *(1)* was isolated as bronze-colored platelets (hexane), m. p. 257—259 °C; UV (CH_2Cl_2): $\lambda_{max} = 484$ nm ($\log\varepsilon = 4.21$); 471 (3.50); 461 (3.21); 454 (3.27); 444 (3.17); 432 sh (2.75); 423 (2.75); 410 (2.89); 358 (3.64); 344 (4.26); 334 (4.14); 299 (4.30); 285 (4.46); 267 (4.99); 254 (4.70).

Under the same conditions we found 2-dimethylamino-1-dimethylaminopropenylidene-3-dimethylimmoniopropenylindene perchlorate *(6)* and cyclopentadiene to give benzo[*a*]pyraceheptylene *(2)* in 2.5% yield. *(2)*, blackish brown needles (hexane), m. p. 198—200 °C; UV (CH_2Cl_2): $\lambda_{max} = 498$ nm ($\log\varepsilon = 3.84$); 485 (3.98); 464 (3.66); 453 (3.54); 422 (3.09); 387 (4.28); 369 (3.94); 348 (4.06); 342 sh (4.02); 300 (4.82); 291 sh (4.75); 286 sh (4.74); 272 sh (4.78); 263 (4.88); 253 (4.87); 237 (4.81).

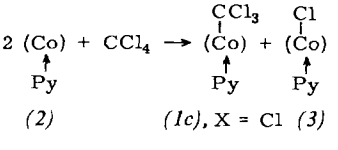
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[1] Cobaloximes are bis(diacetyldioximato)cobalt complexes; cf. *G. N. Schrauzer*, Accounts Chem. Res. *1*, 97 (1968).

[2] The halomethylcobaloximes *(1a)*, *(1b)*, and *(1d)* can be prepared by the known method [3] of reaction of di- and trihalomethanes or CF_3I with cobaloximes(I): The sole limitation is that the reaction medium should not be too strongly alkaline, cf. Inorg. Syntheses *11*, 61 (1968).

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[4] Trihalomethylcobaloximes *(1c)* are not accessible by the method given in Ref. [2]; they are formed, however, from cobaloximes(II) [3] and tetrahalomethanes in CH_2Cl_2 as solvent. To prepare, *e.g. (1c)*, X = Cl, compound *(2)* (10 g) is suspended in CH_2Cl_2 (50 ml) with exclusion of air and the stoichiometric amount of CCl_4 is added slowly. After 25 min the reaction mixture is poured into *n*-hexane (200 ml) and the precipitate is filtered off. In order to isolate compound *(3)*, formed according to



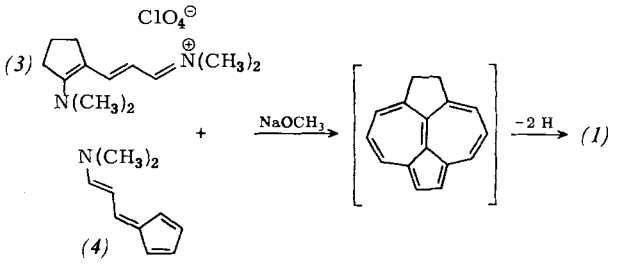
(2) *(1c)*, X = Cl *(3)*

the reaction mixture is washed with water; the insoluble residue is recrystallized from CH_2Cl_2 by addition of *n*-hexane. Compounds *(1c)* decompose gradually on storage and in some cases explode on heating to 120—180 °C. The composition of all the new cobaloximes is established by elemental analysis and NMR spectra.

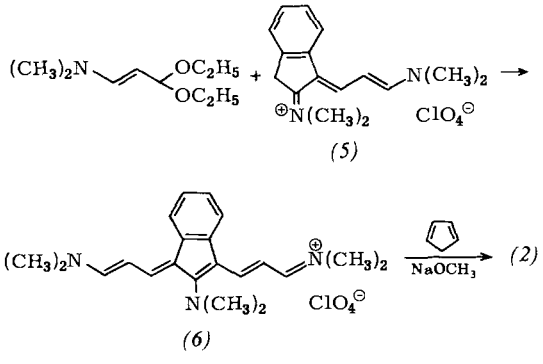
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The mass spectra of *(1)* and *(2)* exhibit very intense molecular ion peaks at *m/e* 202 and 252.



As a preliminary to synthesizing the salt *(6)* we first prepared 1-dimethylaminopropenylidene-2-dimethylimmonioindane perchlorate *(5)*. Compound *(5)*, orange-red needles (acetonitrile), m.p. 245 °C, λ_{max} (CH_3CN) = 474 nm ($\log \varepsilon = 4.84$), is formed in 85% yield from equimolar amounts of 2-dimethylaminoindene[7] and $(CH_3)_2SO_4$-dimethylaminoacrolein adduct in anhydrous ethanol at room temperature.

The ethanol is removed under vacuum after 3 h, the residue dissolved in water, and compound *(5)* precipitated by addition of $NaClO_4$.

Compound *(6)*, black needles (acetonitrile), m.p. 236 to 237 °C, λ_{max} (CH_2Cl_2) = 543 nm ($\log \varepsilon = 4.96$), is obtained from *(5)* in 66% yield on heating with an excess of dimethylaminoacrolein diethylacetal[8] in acetonitrile[***].

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[***] *Note added in proof:* We have prepared *(1)* in 95% yield by reaction of 4,5-trimethyleneazulene with 1-dimethylaminopropene perchlorate.

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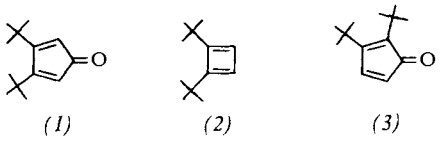
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Direct Proof of Existence of Tetramethylcyclobutadiene[1][**]

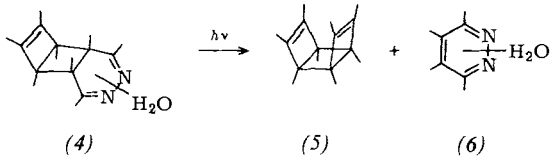
By *Günther Maier* and *Manfred Schneider*[*]

Photocleavage of alkylated cyclobutenedicarboxylic anhydrides in a matrix at −196 °C is accompanied by a yellow coloration which disappears on thawing as soon as the organic glass begins to soften[2]. The long-wave absorption of the matrix (λ_{max} = 410 nm) observed on low-temperature irradiation of 3,4-di-*tert*-butylcyclobutenedicarboxylic anhydride[2] cannot arise only from frozen 3,4-di-*tert*-butylcyclopentadienone *(1)*, which has an absorption maximum at 365 nm, but must be mainly due to another species. The conclusion that this species must be di-*tert*-butylcyclobutadiene *(2)* is compelling, assuming that *(3)*, a positional isomer of *(1)* which has not been isolated but must also be present in the matrix, absorbs below 400 nm like *(1)*.



This assumption has recently been questioned since the cyclopentadienones (2,3,4- and 2,3,5-tri-*tert*-butyl derivatives) formed on photolysis of 2,3,4-tri-*tert*-butylcyclobutenedicarboxylic anhydride[3] exhibit maxima at 415 and 418 nm, respectively. Accordingly, the long-wave absorption found in the di-*tert*-butyl series might possibly also be due to the dienone *(3)*.

Unequivocal spectroscopic proof that the cyclobutadiene system can exist under the above conditions and can be identified by a characteristic UV absorption band is therefore possible only if an independent route is available for the photochemical production of cyclobutadienes. Such a route must avoid cyclopentadienones as reaction products.



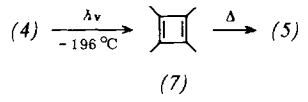
A possible method consists in the photolysis of the tricyclic compound *(4)* [m.p. 172 °C (decomp.); prepared from the parent diacetyl compound[4] with hydrazine; spectra, *e.g.* NMR (CH_2Cl_2): τ = 8.03, 8.33, 8.89, 9.11 (each 6H/s), elemental analysis, and molecular weight are consistent with the proposed structure]. Irradiation of a methylene chloride suspension of *anti (4)* with a low pressure mercury arc lamp proceeded almost quantitatively to give the *syn* tricyclic compound *(5)*[5] and tetramethylpyridazine *(6)* [m.p. 69 °C (decomp.); NMR (CCl_4): τ = 7.52, 7.87 (each 6H/s)].

If *(4)* is irradiated in an EPA matrix (ether, isopentane, ethanol) at −196 °C, a yellow color is also seen which is

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again stable only under these extreme conditions and disappears immediately on removal of the liquid nitrogen coolant. Irradiation products are the hydrocarbon *(5)* and the pyridazine *(6)* (yield >90%). Since *(6)* absorbs at 258.5 nm (in ether) and a charge-transfer complex with tetramethylcyclobutadiene *(7)* is unlikely, the maximum at 375 nm observed on low-temperature irradiation of *(4)* must be assigned to "free" tetramethylcyclobutadiene *(7)*.



(7)

Irradiation of tetramethylcyclobutenedicarboxylic anhydride under the same conditions leads to a broad absorption band (350—600 nm) having a maximum at 425 nm. The reason for the differing electronic spectra—depending upon whether one starts from *(4)* or from the corresponding anhydride—is presumably to be sought in the predominant formation of tetramethylcyclopentadienone on photocleavage of the anhydride, the tetramethylcyclobutadiene being hidden in the short-wave branch of the curve. Alternatively, a donor-acceptor complex between the two compounds may possibly be present in this case.

The exclusive formation of the *syn* tricyclic compound *(5)* on photolysis of *(4)* indicates that tetramethylcyclobutadiene has a singlet ground state. Additional evidence is provided by the low extinction coefficient of the band in the electronic spectrum—we estimate a value of about 200. According to calculations by *Allinger*[6], only two forbidden transitions in the long-wave region are to be expected for singlet cyclobutadiene, while the triplet state should be characterized by a very intense absorption band. In our opinion, the above constitutes the first direct spectroscopic proof of the existence of a "free" alkyl-substituted cyclobutadiene.

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1,3-Dipolar Cycloaddition of Nitrile Oxides to Cyclic Imidic Esters and Amidines

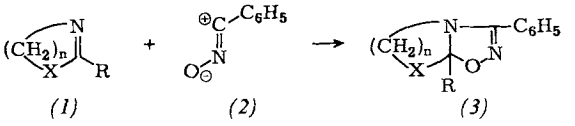
By *Karl-Heinz Magosch* and *Roland Feinauer*[*]

Dedicated to Professor Karl Hamann on the occasion of his 65th birthday

Nitrile oxides undergo 1,3-dipolar cycloaddition to numerous unsaturated systems to give derivatives of 1,2-oxazole[1]. Cycloadditions of cyclic imidic esters and amidines with, *e.g.*, epoxides are also known[2].

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We have studied the reaction of nitrile oxides with cyclic imidic esters and amidines and found that novel bicyclic 1,2,4-oxadiazole derivatives *(3)* result from benzonitrile oxide and oxazol-2-ines, 5,6-dihydro-4*H*-1,3-oxazines, imidazol-2-ines, and 1,4,5,6-tetrahydropyrimidines.



(1) *(2)* *(3)*

n	X	R	yield (%) [a]	*(3)* m. p. (°C)
2	O	CH_3	87	64
3	O	CH_3	26	87
3	N—CH_3	CH_3	32	100
3	N—C_2H_5	CH_3	41	95
3	N-*n*-C_4H_9	CH_3	31	37

[a] Yields not optimized.

Benzohydroxamoyl chloride can be used as starting material instead of benzonitrile oxide *(2)* and converted into the latter immediately prior to reaction with *(1)* by treatment with triethylamine[1].

In order to produce the compounds *(3)*, the reactants *(1)* and *(2)* are allowed to react at 0°C (5 h) in a suitable solvent, *e.g.* diethyl ether; the resulting hetero bicyclic compounds *(3)* are subsequently isolated by evaporation and crystallization. The colorless compounds *(3)*, which readily crystallize, are easily hydrolyzed by aqueous acids and aqueous alkali. Their structure is established by elemental analysis and IR and NMR spectra.

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Perfluoroalkanesulfinic Acids

By *Herbert W. Roesky*[*]

Perfluoroalkanesulfinic acids have not previously been isolated.

We have now found that perfluoroalkanesulfonyl fluorides *(1)* are reduced by hydrazine and that hydrazinium salts *(2)* are formed[1] which contain sulfur having an oxidation number of +4.

$$2R{-}SO_2{-}F + 5N_2H_4 \rightarrow 2R{-}S(O)O[N_2H_5] + N_2 + 2[N_2H_5]F$$

(1) *(2a)*, R = CF_3; *(2b)*, R = *n*-C_4F_9

Compounds *(2)* are soluble in diethyl ether and can thus be separated from hydrazinium fluoride. On reaction with

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an excess of concentrated sulfuric acid they yield the corresponding perfluoroalkanesulfinic acids. For $CF_3S(O)OH$, the ^{1}H-NMR and ^{19}F-NMR spectra provided the following data: $\delta_H = -11.0$ ppm (singlet, external standard $(CH_3)_4Si$), $\delta_F = 78.0$ ppm (singlet, external standard $CFCl_3$). The most striking difference from the already well-known perfluoroalkanesulfonic acids[1] is in the IR spectra: on comparing the spectra, the expected absence of an asymmetric (S=O) stretching vibration[2] is observed in the case of sulfinic acids. The spectrum of $CF_3S(O)OH$ shows bands at 2900 (vs), 2450 (s), 1700 (s), 1185 (vs) with shoulder at 1160, 1095 (vs), 850 (s), 750 (w), 635 (w), 587 (m), 480 (m), and 440 (s) cm^{-1}. The perfluoroalkanesulfinic acids investigated ($CF_3S(O)OH$, b.p. 26—28 °C/0.1 torr) could be characterized by elemental analysis. They are water-clear liquids that do not react with glass and can be vacuum distilled without decomposition.

Preparation of n-$C_4F_9S(O)OH$

Diethyl ether (1400 ml) and anhydrous hydrazine (22 g) are transferred to a three-necked flask fitted with KPG stirrer, dropping funnel, and reflux condenser (with drying tube). n-$C_4F_9SO_2F$[3,4] (60 g) is added dropwise to the stirred mixture at room temperature. A white precipitate is formed and nitrogen is evolved. The ethereal phase is separated from the precipitate and evaporated under vacuum. 12 g of compound *(2b)* remains. Concentrated sulfuric acid (30 ml) is added to *(2b)* (10 g) and the resulting sulfinic acid is distilled off under vacuum (oil-pump; flask temperature 60 °C): b.p. 40—42 °C at 0.05 torr; yield: 7.5 g.

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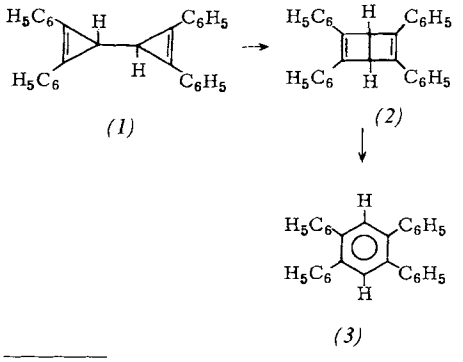
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A New Route to Dewar-Benzenes

By *Robert Weiss* and *Clemens Schlierf*[*]

The thermal rearrangement of bicyclopropenyls *(1)* to benzene derivatives discovered by *Breslow*[1,2] is of considerable mechanistic and preparative interest. We have investigated whether this reaction can be catalyzed by transition metals.



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If a solution of equimolar amounts of *(1)* and $AgClO_4$ in anhydrous acetonitrile is heated to boiling, the occurrence of the rearrangement *(1)*→*(2)*→*(3)* can be established by ^{1}H-NMR spectroscopy. After one hour's reaction the singlet of the bridgehead protons of *(1)* at $\tau = 7.60$ has been completely replaced by a sharp singlet at $\tau = 5.78$, which we assign to the hitherto unknown 2,3,5,6-tetraphenyl-Dewar-benzene *(2)*[3]. The reaction can also be followed in an NMR sample tube and proceeds quantitatively within the limits of detection of NMR; in particular, no evidence is found for the formation of the intermediates tetraphenylprismane and 1,2,3,4-tetraphenyl-Dewar-benzene assumed by *Breslow*[1].

The class of rearrangements Dewar-benzene→benzene is known to be catalyzed by transition metals[5]; accordingly, compound *(2)* rearranges to *(3)* under the above conditions. The NMR spectrum indicates that *(2)* is accompanied by 25% of *(3)*. This finding also shows that the rearrangement *(1)*→*(2)* proceeds more rapidly than *(2)*→*(3)*.

(2) could be isolated pure by column chromatography on basic Al_2O_3 (yield 45%) and characterized: ^{1}H-NMR: $\tau = 2.3$—2.8 (20 H/m); $\tau = 5.78$ (2 H/s); UV: $\lambda_{max}(CH_3CN) = 292$ nm ($\log\varepsilon = 4.38$). For comparison: *cis*-stilbene has $\lambda_{max}(C_2H_5OH) = 290$ nm ($\log\varepsilon = 4.0$)[6]; m.p. 156 °C (Kofler bench); on melting it is converted into 1,2,4,5-tetraphenylbenzene *(3)* of m.p. 268 °C (identical with authentic sample)[7]; $t_{1/2}$ for the thermal rearrangement *(2)*→*(3)* in boiling $CDCl_3 = 15.5$ h.

Preliminary experiments with various substituted bicyclopropenyls suggest that the new rearrangements is of a general nature. Mechanistic details are currently under study.

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New Method of Polypeptide Synthesis

By *Manfred Mutter*, *Hanspaul Hagenmaier*, and *Ernst Bayer*[*]

The use of insoluble, polymeric carriers has simplified peptide synthesis since the soluble reagents present in excess can be removed by filtration[1]. However, the coupling reactions do not usually proceed quantitatively, thus giving rise to failure sequences which can be separated from the final product only with difficulty, if at all[2,3]. Moreover, synthesis on an insoluble carrier permits less

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freedom regarding choice of solvents, protective groups, and coupling method than peptide synthesis in solution. Even the use of solid carriers having ordered surfaces ("brush carriers")[4, 5] or uncrosslinked polystyrenes[6–8] cannot avoid these difficulties entirely.

We have now developed a synthesis in homogeneous phases which permits a definite and simple separation of reagents from the growing peptide chain. A solubilizing protective group is bound to the C-terminal amino acid where it remains for the duration of the synthesis. Polymeric protective groups can be chosen which make the molecule soluble in the desired solvents. In practice, polyethylene glycol residues which can form an ester-type bond with the C-terminal acid have proved particularly effective. The first amino acid as well as the following ones can be linked in homogeneous solution.

The decisive second step of the process, the separation of the low-molecular-weight reagents from the growing peptide chain, which has polymeric character right from the start owing to the protective group, is carried out by ultrafiltration (membrane filtration)[9].

The synthesis has the following advantages: Synthesis and removal of excess reagents in a homogeneous phase can be carried out without the time-consuming separations of "classical" peptide syntheses and the repeated washings of the solid phase method; higher yields than when working in heterogeneous phases; possibility of removing incomplete sequences after each unsatisfactory coupling step; easy assessment of the coupling yield in aliquot amounts (^{19}F-NMR[10] and radioactivity measurements especially suitable); possibility of repeating a coupling step by any other desired method if yields prove unsatisfactory; possibility of condensing larger peptides bearing the macromolecular protective group[11]; possibility of automation, including yield monitoring.

The technique will be explained on the basis of two syntheses of the tetrapeptide H-Ile-Ala-Val-Gly-OH.

1. *Synthesis with tert-butyloxycarbonyl-protected amino acids by the anhydride method*[2]:

Esterification with the soluble carrier: Polyethylene glycol (M. W. 20000) was used as soluble polymer. Esterification is carried out with BOC-protected glycine and with 1,1'-carbonyldiimidazole as coupling reagent[13].

Synthetic cycle: a) Preparation of the mixed anhydride of isobutyl chloroformate and the BOC-protected amino acid with addition of *N*-methylmorpholine[12]. b) Addition of a three-fold excess of the mixed anhydride to the amino component (polymer-peptide). c) After coupling: Removal of protecting group by 4 N HCl in dioxane. d) Removal of solvent by distillation and dissolution in water. e) Ultrafiltration to remove excess components and distillation to remove water.

Conversion test: Aliquots of the reaction mixture are taken during coupling and analyzed by the ninhydrin method[14]. The coupling steps give yields in excess of 98%. The coupling of alanine to valine, which is possible in yields of only about 80% by the solid phase method, also gives a yield of over 95%.

Cleavage from carrier and isolation: The tetrapeptide is split off in the homogeneous phase by 0.05 N NaOH[15] and isolated by ion-exchange chromatography on Dowex X-50.

Ultrafiltration: The substance is dissolved in about 50 ml of water (*ca.* 2% solution) and diafiltrated[16]. The ultrafiltrate is tested for amino acids with ninhydrin until no positive reaction occurs. Hitherto, no membranes have been used that are stable to organic solvents[16].

2. *Synthesis in aqueous solution with benzyloxycarbonyl-protected amino acids and a water-soluble carbodiimide:*

Esterification with polyethylene glycol as described for the anhydride method.

Synthetic cycle: a) The amino component is dissolved in a small volume of water and coupled with a Z-protected amino acid. A water-soluble carbodiimide, *N*-[2-(cyclohexyliminomethyleneimino)ethyl]-*N*-methylmorpholinium *p*-toluenesulfonate[17], is used as coupling reagent. Coupling component and Z-amino acid are used in threefold excess. b) After coupling, an equal volume of methanol is added to the aqueous solution and the protective group removed by hydrogenation (Pd/activated charcoal). c) Ultrafiltration as well as cleavage and isolation of the tetrapeptide are carried out as described for the anhydride method.

The new method combines the advantages of the Merrifield solid phase synthesis and "classical" peptide synthesis. The effect of macromolecular C-terminal protecting groups on solubility and coupling opens up new preparative possibilities extending beyond the bounds of this method.

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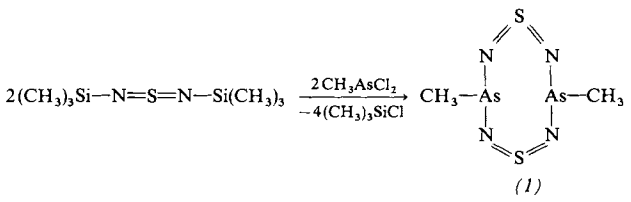
$(CH_3As)_2S_2N_4$—A Novel Arsenic-Sulfur-Nitrogen Heterocycle

By *Otto J. Scherer* and *Reinhard Wies*[*]

Formally, 3,7-dimethyl-1,5,2,4,6,8,3,7-dithia(IV)tetrazadiarsocine *(1)* can be visualized as tetrasulfur tetranitride (S_4N_4)

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in which two sulfur atoms have been replaced by CH_3As groups. It is formed in 76% yield by cleavage of the Si—N bonds[1] of *N,N'*-bis(trimethylsilyl)sulfur diimide by CH_3AsCl_2.



(1)

(1) is a red liquid (glass-like solid at low temperature), which is sensitive to hydrolysis, is very soluble in ether, benzene, and carbon tetrachloride, and moderately soluble in hexane; it can be distilled without decomposition at b. p. 84—86 °C/0.05 torr. Prolonged heating at 110—120 °C leads to slight decomposition[2].

Reaction of *(1)* with SCl_2 in molar concentrations of 1:2 affords, in addition to CH_3AsCl_2, about 40% S_4N_4.

Compound *(1)* was characterized by means of complete elemental analysis, cryoscopic molecular weight determination (in benzene; found: 294; calc.: 300) and by ^{1}H-NMR, IR, UV, and mass spectroscopy.

^{1}H-NMR (60 MHz; 10% CCl_4 solution; TMS int.): singlet at $\delta(CH_3As) = -106$ Hz. Mass spectrum (16 eV)[3]: *m/e* 300, molecular ion (100); 285, $CH_3As_2N_4S_2$ (92); 136, CH_3AsNS (8). None of the additional fragments has a relative intensity >1. IR (capillary film between KBr plates): The bands at 1043, 1066, and 1190 cm^{-1} have tentatively been assigned to the NSN system. UV (in hexane): λ_{max}(nm) 242 ($\varepsilon = 15400$), 302 (2300), 405 (419).

Experimental

Methyldichloroarsane (5.5 g, 34 mmol) is added dropwise in an atmosphere of nitrogen into a rapidly stirred solution of *N,N'*-bis(trimethylsilyl)sulfur diimide[4] (7.0 g, 34 mmol) in ether (50 ml). As reaction proceeds, the yellow solution gradually turns orange and a small amount of yellow precipitate separates out. After filtration through a G3 frit, solvent and trimethylchlorosilane are sucked off under vacuum (water pump). The residue is then fractionally distilled under vacuum (oil pump). Yield 3.9 g (76%).

Received: June 1, 1971 [Z 498 IE]
German version: Angew. Chem. *83*, 882 (1971)

[1] Cf. *O. J. Scherer*, J. Organometal. Chem. Rev. *A 3 (1968)*, 281.

[2] In contrast to S_4N_4 and S_4N_2, compound *(1)* is not explosive.

[3] We thank Dipl.-Chem. *N. Pelz* for the measurements.

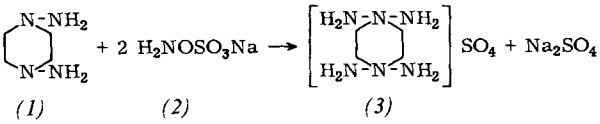
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Preparation of *N,N,N',N'*-Tetraaminopiperazinium Salts[**][1]

By *Karl-Heinz Linke* and *Ralf Turley*[*]

Although the onium salts of triazane, N_3H_6X, are extraordinarily unstable[2], the triazanium salts with organic substituents exhibit a relatively high stability[3-5]. We have been able to prepare *N,N,N',N'*-tetraaminopiperazinium sulfate *(3)* by exhaustive amination of *N,N'*-diaminopiperazine *(1)* with the sodium salt of hydroxylamido-*O*-sulfuric acid *(2)*. This is the first reported synthesis of a bis(triazanium)salt.

The chloride *(4)* and the azide *(5)* could be prepared by reaction of *(3)* with barium chloride and barium azide, respectively, in aqueous medium. The salts *(3)*, *(4)*, and *(5)* are colorless and crystalline: *(3)*, m. p. 144 °C (dec.); *(4)*, m. p. 156 °C (dec.); *(5)*, m. p. 128 °C (dec.). They are



(1) *(2)* *(3)*

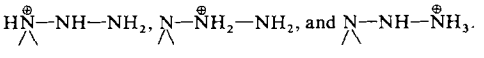
only very slightly soluble in the usual organic solvents and moderately soluble in neutral aqueous solutions. They can be stored indefinetely in the solid state or in neutral aqueous solution.

Characterization of the compounds follows from IR spectroscopic analysis (see Table) and elemental analysis.

Table. Most intense IR bands of cations in the salts *(3)*, *(4)*, and *(5)*.

Vibrational mode	IR (cm^{-1}) *(3)*	*(4)*	*(5)*
ν_{as} NH_2	3230	3205	3230
ν_s NH_2	3110	3110	3110
δ NH_2	1630, 1610	1635, 1595	1630, 1610
γ NH_2	1150	1150	1150
ν NN	910	910	910
ν NNH_2	715	730	730

Proof of the given structure of the cation is afforded by the mode of reaction, since the aminating reagent always attacks at the most basic nitrogen atom. Further evidence is provided by the absence of the $\equiv\overset{\oplus}{N}H$-, $=\overset{\oplus}{N}H_2$-, or $-\overset{\oplus}{N}H_3$ bands, which one would expect[4] to find in the IR spectra between 2200 and 2700 cm^{-1} in the case of the other three theoretically possible structures for the triazine groups:



N,N,N',N'-Tetraaminopiperazinium sulfate (3)

An ice-cold solution of *(2)*, prepared by careful neutralization of an aqueous solution of hydroxylamido-*O*-sulfuric acid [11.3 g (0.1 mol) in 50 ml H_2O] with aqueous sodium hydroxide [4.0 g (0.1 mol) in 50 ml H_2O], is added dropwise over 10 mins with vigorous stirring to a warm (80 °C) aqueous solution of *(1)* [5.8 g (0.05 mol) in 300 ml H_2O]. The reaction mixture is evaporated down to 80 ml under reduced pressure and the crystals which precipitate are

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

[1] Chemistry of hydrazine and its derivatives, Part 32.—Part 31: *K.-H. Linke* and *D. Skupin*, Z. Naturforsch., in press.

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[6] *R. Gösl* and *A. Meuwsen*, Chem. Ber. *92*, 2521 (1959).

filtered off and washed with ice-cold water (20 ml); yield 4.5 g (37%). On further evaporation of the mother liquor an additional crop of *(3)* can be obtained but this is contaminated with sodium sulfate. *(1)* was prepared for the first time by direct amination of an equivalent amount of *(2)*—thus supporting the work reported in Ref. [6]; yield *ca.* 20%.

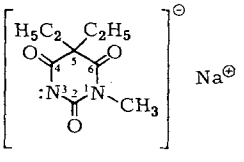
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German version: Angew. Chem. *83*, 884 (1971)

Intermolecular Interactions in the Crystal Structure of the Hydrogen-Bond-Free Barbiturate Sodium Metharbital

By *Bernhard Berking*[*]

In the crystal structures of barbiturates and their derivatives that have been investigated so far, the packing of the molecules in the unit cell is established by one or more of the following intermolecular interactions: effective packing of alkyl groups, coordination of cations, dipole-dipole interaction, and, predominantly, by extended systems of hydrogen bonds. If in the latter case, the hydrogen atoms on C(5) are substituted, the imino nitrogen atoms in the pyrimidine ring usually serve as donors and the exocyclic oxygen atoms as acceptors—as, for example, in the barbital I and II structures[1].

The crystal structure of sodium 1-methyl-5,5-diethylbarbiturate (also called sodium metharbital or sodium



gemonil) was determined since in this case N(1) is methylated and N(3) deprotonated; consequently, hydrogen bonding is, *a priori*, not possible and the other types of bonding become effective.

As in the sodium[2] and calcium[3] salts of barbital (5,5-diethylbarbiturates) the deprotonation of the trioxopyrimidine ring at the imino nitrogen atom N(3) causes a shortening of the endocyclic C—N(3) bonds and a stretching of the adjacent exocyclic C=O bonds:

N(3)—C(2)	1.339 Å	C(2)—O(2)	1.240 Å
N(3)—C(4)	1.342 Å	C(4)—O(4)	1.233 Å
N(1)—C(2)	1.417 Å	C(6)—O(6)	1.225 Å
N(1)—C(6)	1.362 Å		

Comparable values in free barbituric acid are 1.37 Å for C—N bonds and 1.21 Å for C=O bonds (mean values)[1]. It can therefore be concluded that there is a redistribution of the formal negative charge over the anion—namely to the oxygen atoms, particularly the two oxygen atoms adjacent to N(3). Of special interest, therefore, is the remaining electronegativity of the deprotonated nitrogen atom and its ability to coordinate the sodium ion.

Figure 1 shows the packing of the molecules in the unit cell. All the ethyl groups lie in hydrophobic channels; the

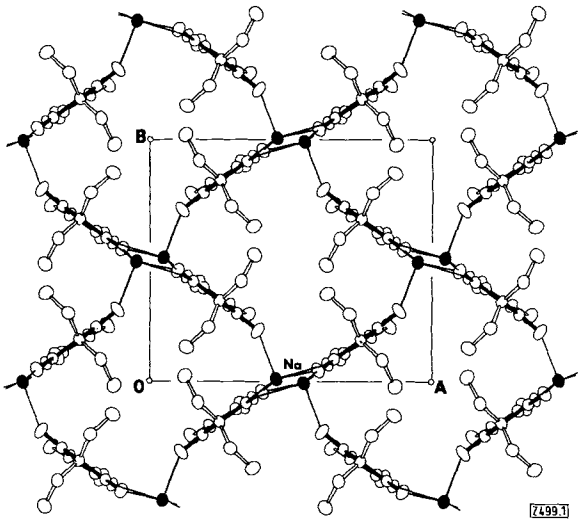


Fig. 1. Packing of sodium metharbital molecules in the unit cell.

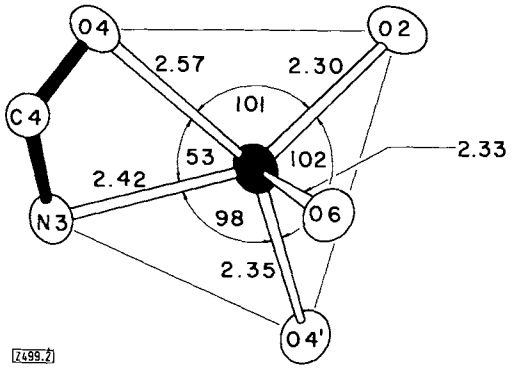


Fig. 2. Coordination of the sodium ion (black) in the sodium metharbital lattice [bond lengths Å, angles (°)].

van der Waals interactions are weak: no intermolecular distance is less than 2.45 Å, eight are smaller than 2.70 Å. All the oxygen atoms are situated in hydrophilic regions together with the sodium ion.

As can be seen in Figure 2, the sodium ion is fivefold coordinated: three oxygen atoms and the deprotonated nitrogen atom form the base and oxygen atom O(6) the apex of a pyramid which is surrounding the sodium ion. The coordination polyhedron can also be described as a tetrahedron with one corner replaced by the rigid intramolecular group N(3)—C(4)=O(4). The polyhedra are linked by sharing corners. Three of the Na—O distances have expected values, *i.e.* in the range 2.30—2.35 Å, but one (Na—O(4)) with a value of 2.57 Å is exceptionally large. A Na—N distance of only 2.42 Å has not been reported so far.

Na ions are preferably coordinated by oxygen atoms and not by nitrogen atoms. Thus, *e.g.*, in the structure of sodium barbital[2] the Na^+ ion is surrounded by an almost regular tetrahedron (d_{Na-O} = 2.31—2.35 Å) while the deprotonated nitrogen atom (d_{Na-N} = 2.80 Å) does not take part in intermolecular interactions.

In the few cases of coordination by nitrogen, no Na—N distance of less than 2.5 Å has been found, even in structures such as NaN_3[4, 5] and $NaCl \cdot 5^1/_7\ NH_3$[6] in which com-

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peting oxygen atoms are absent. These structures exhibit comparably short bond lengths of 2.44 and 2.37 Å, respectively, only in other modifications at low temperatures.

The short Na—N and the extra long Na—O(4) distances in sodium metharbital suggest that the Na—N interaction is not a result of rigid intermolecular grouping N(3)—C(4)=O(4), in which coordination is actually by O(4), but that the electronegativity of the deprotonated nitrogen atom is itself not inferior to that of the oxygen atoms.

Sodium metharbital crystallizes in the orthorhombic space group $Pna2_1$ with $a=12.670$, $b=10.796$, $c=7.802$ Å, $Z=4$, and $D_m=1.369$ g/cm³. 962 X-ray reflections were recorded on an automatic diffractomer. The structure was solved by direct methods, and the refinement converged at $R=0.023$ with a standard deviation of 0.002 Å for the quoted bond lengths.

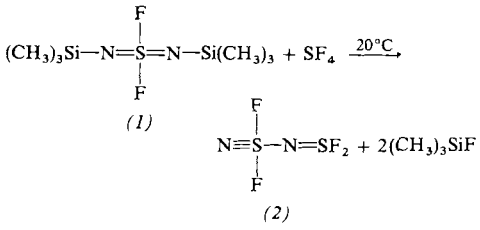
Received: June 4, 1971 [Z 499 IE]
German version: Angew. Chem. 83, 889 (1971)

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[3] *B. Berking,* Acta Crystallogr., in press (1971).
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[5] *S. B. Hendricks* and *L. Pauling,* J. Amer. Chem. Soc. *47,* 2904 (1925).
[6] *I. Olovsson,* Acta Crystallogr. *18,* 879 (1965).

N-(Nitridofluorosulfur)sulfur imide difluoride

By *Oskar Glemser* and *Rainer Höfer*[*]

Bis(N-trimethylsilylimido)sulfur difluoride *(1)*[1], which is formed in the reaction of sulfur nitride trifluoride NSF_3 with lithium bis(trimethylsilyl)amide, reacts with sulfur tetrafluoride in an autoclave to give *(2)* in accordance with the following equation:



(2) is the first sulfur-nitrogen compound to be prepared containing SN single, double, and triple bonds. It reacts vigorously with water and readily decomposes at room temperature. The composition of *(2)* was established by elemental analysis and its structure has been confirmed by NMR, IR, and Raman spectroscopy.

^{19}F-NMR (ext. $CFCl_3$): $\delta(-N{=}SF_2)=-37.2$ ppm (triplet); $\delta(N{\equiv}SF_2-)=-101.5$ ppm (triplet) at -25 °C; $^4J_{FF}=4.2$ Hz. IR (cm^{-1}): 1470 (s) ($\nu_{S\equiv N}$), 1222 (vs) ($\nu_{S=N}$), 1085 (w), 1008 (w), 868 (m), 815 (m), 779 (vs), 659 (m), 587 (w), 445 (w), 414 (m). Raman (cm^{-1}): 1475 p ($\nu_{S\equiv N}$), 1203 p ($\nu_{S=N}$), 1043 dp, 829 p, 726 dp, 662 p, 590 p, 414 p, 381 dp, 273 dp. Mass spectrum (rel. intensity): molecular ion NSF_2—NSF_2^+ (90), NSF_2NSF^+ (2), NSF_2NS^+ (3), NSF_2^+ (50), SF_2^+ (100), NSF^+ (30), SF^+ (70), NS^+ (92).

Two weak signals (quintet and triplet) in the ^{19}F-NMR spectrum and additional fragments in the mass spectrum (SF_4—NSF_2^+, SF_2—NSF_2^+, and SF_3^+) suggest the existence of a further compound, which probably is to be formulated as $F_2S{=}N{-}SF_4{-}N{=}SF_2$; it is present in the reaction mixture to the extent of about 1%.

Experimental

SF_4 (18.0 g, 0.167 mol) is carefully condensed (liq. air) in an autoclave containing *(1)* (16.1 g), (0.066 mol). After thawing-out, the reaction mixture is stirred for 24 h at room temperature and finally fractionally distilled under high vacuum. Yield of *(2)*: 6 g (56%); m.p. -25 °C.

Received: June 24, 1971 [Z 500 IE]
German version: Angew. Chem. 83, 890 (1971)

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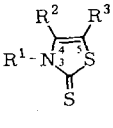
CONFERENCE REPORTS

Reactivity and Conformation in the Heterocyclic Series.—The Gear Effect

By *Jacques Metzger*[*]

The influence of conformation on chemical reactivity and NMR spectra was described for the case of Δ4-thiazolin-2-thiones. With 3,4-dialkyl-Δ4-thiazolin-2-thiones *(1a)*, which are accessible from α-halogenated ketones and *N*-alkyldithiocarbamates, dealkylation is observed from the nitrogen atom if N-3 carries a *tert*-butyl group and C-4 a methyl or larger alkyl group.

A simple calculation of the van der Waals interaction energy by *Westheimer*'s method affords a good correlation between this energy and the anomalous reaction.



(1a), $R^1 = R^2 =$ Alkyl, $R^3 =$ H
(1b), $R^1 =$ Isopropyl, $R^2 =$ Alkyl, $R^3 =$ H
(1c), $R^1 = R^2 =$ Alkyl, $R^3 =$ Methyl

For 4-alkyl-3-isopropyl-Δ4-thiazolin-2-thiones *(1b)* the shape of the NMR signal of the methyl protons of the isopropyl group depends on the substituent at C-4: if $R^2=H$,

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CH_3, C_2H_5, $(CH_3)_2CH$, or $(CH_3)_3C$, a sharp doublet, a broad doublet, an unresolved broad signal, two poorly resolved doublets, and a very sharp doublet are observed at room temperature. This result can be simply explained on the basis of the calculated relative energies of the possible conformations of the molecule.

Introducing a methyl group at C-5 [compound *(1c)*] greatly alters the ratio of the conformers that differ in arrangement around N-3. We call such an indirect conformational interaction a "gear" effect. In general, this effect is found when the ratio of the conformers differing in arrangement at atom 'a' is altered by the substituents on atom 'c', the effect operating through and beyond atom 'b'. It may well contribute to an understanding of several hitherto unsolved conformational problems.

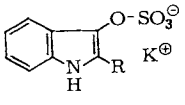
Lecture at Hamburg (Germany) on June 11, 1971 [VB 313 IE]
German version: Angew. Chem. *83*, 808 (1971)

Biological Precursors and Genesis of Tyrian-Purple

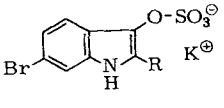
By *Herbert Fouquet* and *Hans-Joachim Bielig* (Lecturer)[*]

It has been known for some time that indigo[1] and 6,6'-dibromo indigo[2] are major constituents of the ancient dye Tyrian purple (red = purpura blatta, blue = purpura hyacinthina, and violet-red = purpura dibapha) from gastropod mulluscs (Murex, Purpura, and other species). Living gastropod mulluscs contain no indigoid dyes however. They are formed, as previously assumed, by the action of atmospheric oxygen and light on the autolyzed hypobranchial glands. An enzyme (purpurase) also plays an important role in this transformation[3,4]. *Letellier*'s attempts at isolating chromogens from *Purpura lapillus* Lam. (Atlantic)[5] yielded two photolabile components (water-soluble leuco- and ether-soluble chlorolapillin), which afford dyes at different rates, in addition to photostable alkali-soluble xantholapillin. The analog of leucolapillin obtained from the hypobranchial glands of *Murex brandaris* or *M. trunculus* L. (Mediterranean) can be separated into one or two prochromogens which on acid hydrolysis afford sulfate, or sulfate and a thiol, as well as indigoid and bromoindigoid dyes[6].

We[7] have now been able to establish that four chromogens are always present (average total 1.2 mg/gland, in the ratio *(1)*:*(2)*:*(3)*:*(4)* ≈ 4.5:0.5:3:2) in methanol extracts of *Murex trunculus* and usually only one of these (up to 0.6 mg (4)/gland) in extracts of *M. brandis*, *M. erinaceus*, and *P. haemastoma*. The colorless water-soluble crystallates of the chromogens were isolated in pure form by combination of gel chromatography and thin-layer chromatography.



(1), R = H
(2), R = SCH_3



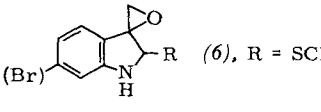
(3), R = H
(4), R = SO_2CH_3
(5), R = SCH_3

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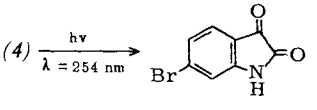
Their structures, *(1)* to *(4)*, were established by elemental analysis, and UV, mass, and NMR spectroscopy. Compound *(5)*, which is missing in this series, was discovered independently in *Dicathais orbita* (Pacific Ocean)[8].

On treatment with Raney nickel in ethanol, compounds *(2)* and *(4)* are converted into *(1)* either directly or *via (3)*. Hydrolysis with hydrochloric acid affords sulfate [like *(1)* and *(3)*] and methanethiol (detected as Hg thiolate by gas chromatography) corresponding to the cleavage observed with phalloidin and α-amanitin[9]. Besides indigo and 6,6'-dibromoindigo, the analogous indirubins and other known red 2,3'-coupled indigoid dyes are formed.

The chromogens *(1)* and *(3)* react anaerobically in the dark at pH = 7.4 with the purpurase recognized as aryl sulfatase to give indoxyl and 6-bromoindoxyl (as indolinones) respectively, which afford aerobically in the dark only indigo and 6,6'-dibromindigo taking up 1 mol O_2/mol dye. The chromogens *(2)* and *(4)*, on the other hand, react aerobically with aryl sulfatase in the dark to give the green ether-soluble quinhydrones (corresponding to *Letellier*'s chlorolapillin) of 2-methylthioindole and 2-methanesulfonyl-6-bromo-indoxyl and their oxidation products (indolenineinones). The last-named can be precipitated as the epoxide-type compounds *(5)* by treatment with diazomethane. In daylight, the green intermediates undergo photolytic cleavage of the *S*-components (to dimethyl sulfide or secondary methanethiols) to give exclusively the same dyes as *(1)* and *(3)*. A total of only 0.5 mol O_2/mol dye is consumed in this combined dark- and light-reaction. If conversion of the chromogens is carried out in the presence of isatin or 6-bromoisatin [*(7)*, *Latellier*'s xantholapillin] also found in purpura glands, formation of the corresponding indirubins additionally takes place. When the chromogen *(4)* is irradiated in the solid phase with 254-nm light it undergoes quantitative photooxidation to compound *(7)*, whereas the chromogen *(2)* is not affected.



(6), R = SCH_3, SO_2CH_3



(7)

It can be concluded from the above findings that the ancient dye purpura blatta originates predominantly from the chromogen *(4)*, *i.e.* from purpura gastropod molluscs of

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[3] Summary in *O. v. Fürth*: Vergleichende chemische Physiologie der niederen Tiere. G. Fischer-Verlag, Jena 1903, p. 373f.
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[5] *A. Letellier*, Arch. Zool. Exper. *8*, 361 (1890).
[6] *S. Bouchilloux* and *J. Roche*, Bull. Inst. Océanogr. [Monaco] Nr. 1054 (1955).
[7] *H. Fouquet*, Dissertation, Universität Saarbrücken 1970; cf. also *J. Malaszkiewicz*, Dissertation, Universität Saarbrücken 1967.
[8] *J. T. Baker* and *M. D. Sutherland*, Tetrahedron Lett. *1968*, 43.
[9] *H. Faulstich* and *Th. Wieland*, Liebigs Ann. Chem. *713*, 186 (1968); *Th. Wieland* and *U. Gebert*, *ibid. 700*, 157 (1966).

the Brandaris type. Purpura hyacinthina preferentially arises from *(1)* and *(3)*, *i.e.* from the Trunculus type, and purpura dibapha from the chromogens of both types by double dyeing. The varied fastness to light was determined by the amount of indirubins produced.

Lecture at Tübingen on July 2, 1971 [VB 315 IE]
German version: Angew. Chem. *83*, 856 (1971)

Modes of Action of Antibiotics

By *Josef Schmidt-Thomé*[*]

In the lecture five important groups of antibiotics, classed according to mode of action, were discussed:

1. Antibiotics which inhibit synthesis of the cell wall. The first and foremost of this group are the penicillins and cephalosporins, which specifically hinder the synthesis of the murein of the cell wall by inhibition of a D-alanyl transpeptidase. Other antibiotics, such as cycloserin, bacitracin, novobiocin, vancomycin, and ristocetin also interfere with the murein synthesis, but in a different manner.

2. Antibiotics which influence the permeability of the cell membrane and thus increase the exit and entry of ions and important cell components. For example, the tyrocidins, polymyxins, polyene antibiotics, alkali metal ionophores such as valinomycin, and the nonactins *etc.* belong to this group.

3. Antibiotics that inhibit the synthesis of important cell components in the interior of the cell, *e.g.* azaserin and diazooxonorleucin, which interfere with purine biosynthesis; also belonging to this group are a series of purine antibiotics such as psicofuranin, angustmycin and cordycepin.

4. Antibiotics which inhibit the synthesis of DNA and RNA. Rifamycins, streptovaricins, and tolypomycin specifically inhibit the DNA-dependent RNA polymerases. A large number of antibiotics react with the DNA template and thus interfere with or inhibit activity of the RNA or DNA polymerases, *e.g.* actinomycins, chromomycins, anthracyclin antibiotics such as rhodomycin, cinerubins, pyrromycins, mitomycins, and porfiromycin *etc.*

5. Antibiotics which inhibit protein biosynthesis. The interaction of mRNA and tRNA with the ribosomes and the enzymes taking part in protein biosynthesis can be disturbed and inhibited at various points by antibiotics. Several antibiotics, some of which are currently being used in therapy, interfere with these complicated processes, *e.g.* tetracyclins, macrolides, chloramphenicol, and aminoglycosides such as streptomycin *etc.*

The lecture concluded with a report on some of the work being carried out at Farbwerke Hoechst on the mode of action of moenomycin and on the application of *in vitro* systems of protein synthesis to specificity investigations of tetracyclin derivatives and other antibiotics.—A knowledge of the effect of antibiotics on vitally important processes in the cell opens up new prospects for future cancer and virus therapy.

Lecture at Tübingen on July 9, 1971 and at Karlsruhe on July 15, 1971 [VB 316 IE]
German version: Angew. Chem. *83*, 808 (1971)

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Polarographic Trace Analysis of Inorganic Substances in Non-Aqueous Solvents (Example: Phosphorus and Silicon)

By *Friedel Pottkamp* and *Fritz Umland* (Lecturer)[*]

Phosphorus and silicon can be selectively extracted as the dodecamolybdato acids (abbreviated PMo and SiMo) with butyl acetate[1]. The acids are polarographically active in the organic phase after addition of ethanolic LiCl solution as supporting electrolyte. In the ppm range (*ca.* 10^{-4} mol/l) two groups of three polarographic waves are obtained which are best resolved by AC rapid polarography; position in volts versus the Ag/AgCl electrode in 1 N ethanolic LiCl solution: 1. −0.14, 2. −0.46, 3. −0.65, 4. −1.29, 5. −1.50, 6. −1.85.

The AC peaks No. 1 and No. 2 correspond to the H^+-dependent waves also occurring in aqueous solution and can be rendered by the following reduction process:

$$H_3[PMo_{12}O_{40}] + nH^{\oplus} + ne^{\ominus} = H_3[PMo_{12}O_{40-n}(OH)_n]$$

where $n=2$ and $n=4$. The signals of the two isomeric forms of dodecamolybdato-silicic acid appear at considerably different positions: 1. α-SiMo: −0.13 V; 2. β-SiMo: −0.30 V. The electrode process responsible for peak 3 is not yet clear; however, it can be stated with certainty that it is not due to reduction of an isopolymolybdic acid, which accompanies the PMo signal in aqueous solution.

In the case of the more negative group of three peaks, a diffusion controlled wave (peak No. 5) occurs at higher LiCl concentrations (*ca.* 4 mol/l) which is flanked by two adsorption controlled waves. These disappear with decreasing LiCl concentration and increasing H^+ concentration. With decreasing LiCl concentration, the wave No. 5 converts to a kinetically controlled limiting current. In the case of PMo it is a matter of a catalytic H^+ reduction, which permits an accurate determination of P in the ppb range ($3\sigma = 2 \times 10^{-11}$ mol/l).

The catalytic H^+ discharge at a substantially more positive potential than the discharge of stronger acids resembles the H^+ discharge catalyzed by organic ammonium ions that was reported by Nürnberg[2].

As distinguished from the ammonium depolarizers, however, the H^+ reduction catalyzed by PMo is dependent not only on the K_s value but also on other properties of the acid. Thus, the catalytic wave is obtained with PMo + acetic acid but not with PMo + chloroacetic acid.

Consequently, a complex associate or solvate of (reduced) PMo and acetic acid occurring as oxonium ion must be assumed to act as depolarizer.

Lecture at Bonn on June 22, 1971 [VB 317 IE]
German version: Angew. Chem. *83*, 809 (1971)

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[1] *F. Umland* and *G. Wünsch*, Z. Anal. Chem. *225*, 362 (1967).

[2] *H. W. Nürnberg* and *M. v. Stackelberg*, J. Electroanal. Chem. *2*, 350 (1961); summary given therein.

General Meeting of the Gesellschaft Deutscher Chemiker 1971

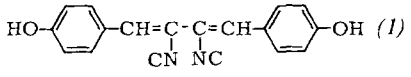
This year's General Meeting was held at Karlsruhe (Germany) from 13th to 18th September. A selection of abstracts of the lectures and discussions that took place on this occasion is given below. Only work that has not been published or presented for publication is included. The abstracts are listed in the alphabetical order of authors names.

From the lectures:

Studies of the Biogenesis of Xanthocillin

By *Hans Achenbach* (Lecturer) and *Franz König*[*]

Xanthocillin *(1)* is characterized by a symmetrical 1,4-diarylbutadiene skeleton to which two isocyano groups are attached at positions 2 and 3.



(1)

Tracer experiments with doubly labeled tyrosine showed that this amino acid can be incorporated into *(1)* as an intact C_6—C_2—N unit. Mass-spectrometric isotopic analysis of *(1)* after addition of [^{15}N]tyrosine led to a surprising result: only one of the nitrogen atoms in the two isocyano groups arises from tyrosine.

This and other experimental results contradict the biogenetic equivalence of the two symmetrical halves of the xanthocillin molecule. They suggest that some other amino acid is concerned in the formation of the isocyano groups.

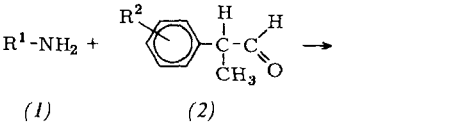
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Relation of Imine-Enamine Tautomerism to Structure

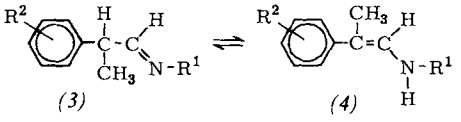
By *Hubertus Ahlbrecht*[*]

The condensation products of primary aromatic and aliphatic amines *(1)* with hydratropaldehydes *(2)* that are substituted in the benzene nucleus tautomerize in solution to mixtures of imine *(3)* and enamine *(4)*.

The position of the equilibrium is dependent on the solvent and the temperature. It is also strongly influenced by substituents on the nitrogen (R^1) and in the β-benzene ring (R^2). Study of the dependence on substituents showed that any structural change that tends to remove electrons from the enamine system leads to stabilization of the enamine form. The influence of a substituent in the β-benzene nucleus is thus described very nicely by the Hammett σ value. This is no longer true for substituents on an *N*-phenyl group; with *para*-substitution direct resonance interactions occur. The latter can be recognized from enthalpy/entropy diagrams. The values of the enthalpy and entropy changes were determined from the temperature-dependence of the equilibria; they showed that in the systems studied the enamine formation is in general exothermic and involves loss of entropy and that the equilibrium is enthalpy-controlled.



(1) *(2)*



(3) *(4)*

R^1: alkyl or aryl; R^2: OCH_3, CH_3, CH_3, Cl, Br, or NO_2

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Fluorescence and Fluorescence Thermochromism of Copper(I) Compounds

By *Heinz D. de Ahna* (Lecturer) and *H.-D. Hardt*[*]

Reduction of copper(II) acetate in acetonitrile/acetic acid by hydrazine hydrate with exclusion of oxygen leads to solutions of copper(I) acetate, from which very pure microcrystalline copper(I) halides are precipitated on addition of an acetyl halide (=AcX):

$$Cu(OOC{-}CH_3)_2 \xrightarrow[CH_3CN/CH_3COOH]{\Delta,\ N_2H_5OH} CuOOC{-}CH_3 \xrightarrow{AcX} CuX$$

On treatment with pyridine or alkylpyridines (=L) these halides form yellow to greenish-yellow compounds of composition $Cu(L)_3X$.

From these can be obtained, by controlled thermal decomposition, colorless compounds of composition Cu(L)X. All these compounds show an intense fluorescence of the most varied colors.

Some compounds of the composition Cu(L)X change their fluorescence color reversibly at low temperature, *e.g.*, Cu(2-picoline)Br from red to blue. The term "fluorescence-thermochromism" is proposed for this phenomenon.

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Crystallo-Chemical Aspects of the Gas-Phase Synthesis of Icosahedral Boro- and Boride-Structures

By *Eberhard Amberger*[*]

When the pyrolysis of pure borohalides and H_2 is carried out at a temperature in the range in which crystal growth is dependent on the kinetics (900—1500 °C), separation of elemental boron takes place: besides glassy-amorphous boron, only two lattices of the long series of lattices described in the literature as "boron modifications" are formed, namely the α-rhombohedral and the II-tetragonal lattices. Since all lattices of boron and boron-

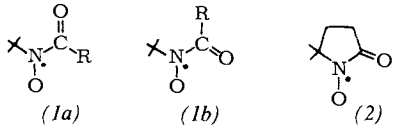
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rich borides contain B_{12} icosahedra as structural units, space-filling is slight. On addition of small amounts of foreign gases ($AlBr_3$, CH_4, $SiBr_4$, N_2, PBr_3) to the synthesis gas individual foreign atoms occupy holes in the lattice. When incorporated in very small amounts, the atoms Al, C, Si, N, and P induce formation of a β-rhombohedral lattice. Incorporation of slightly larger amounts of foreign atoms leads to formation of the I-tetragonal lattice [*e.g.* $(B_{12})_4B_2C$, $(B_{12})_4B_2C_2$, $(B_{12})_4C_3$, $(B_{12})_4B_2N_{1-2}$]. If still larger amounts of foreign atoms are incorporated the rhombohedral angle of the α-rhombohedral cell expands to the "$B_{13}C_2$" cell ("borocarbide structure"; *e.g.* $B_{12}BC_3$, $B_{12}B_{2.45}P_{0.55}$, $B_{12}P_{1.5}$).

ESR Spectroscopic Investigations of Acyl and Azomethine Nitroxides

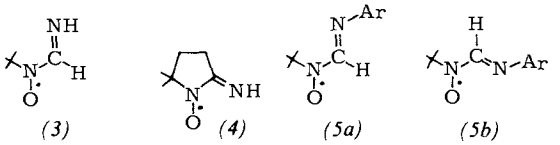
By *Hans G. Aurich* (Lecturer), *Jürgen Trösken*, and *Helmut Forster*[*]

In the ESR spectra of the radicals *(1)*, R = CH_3, C_2H_5, $(CH_3)_2CH$, and $(CH_3)_3C$, the nitrogen coupling constants are substantially unchanged as the size of the group R is increased. It may therefore be assumed that these radicals adopt the *E* conformation *(1a)* and not the *Z* conformation *(1b)*.



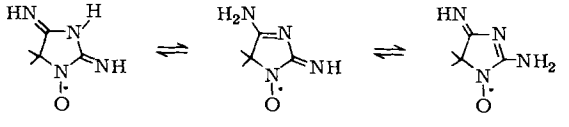
(1a) *(1b)* *(2)*

For *(1)*, R = CH_3, and the nitroxides *(2)*—*(4)* in aprotic solvents the nitrogen coupling constants are found to increase with increasing polarity of the solvent (correlation with E_T values). In protic solvents, however, the expected increase in coupling constants does not occur; this is attributed to preferred formation of hydrogen bonds to the carbonyl or imino group.



(3) *(4)* *(5a)* *(5b)*

However, the ESR spectra of *(5)* in strongly polar solvents show two radical species, from which it can be concluded that both conformations *(5a)* and *(5b)* are present.



(6a) *(6b)* *(6c)*

For the porphyrexide *(6)*, which can exist as *(6a)*—*(6c)*, it was shown by deuteration and labeling of the nitrogen at position 2 by ^{15}N that the forms *(6a)* and/or *(6b)*, with the exocyclic 2-imino group, preponderate in a series of aprotic solvents.

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Conformational Analysis of Organometallic Lanthanoid and Actinoid Complexes by Means of the Paramagnetically Induced Shifts in Their ^{1}H-NMR Spectra

By *Reinhard von Ammon* (Lecturer), *R. Dieter Fischer*, and *Basil Kanellakopulos*[*]

The organometallic complexes $(C_5H_5)_3PrCNC_6H_{11}$ *(1)*, $(C_5H_5)_3UOC_6H_{11}$ *(2)*, and $(C_5H_5)_3UO$-cholesteryl *(3)* show ^{1}H-NMR spectra extended over a wide frequency range. The positive and negative paramagnetic shifts are due to the central metal whose electron relaxation is particularly favorable for NMR investigations because of the f^2 configuration (Pr^{3+}, $4f^2$; U^{4+}, $5f^2$).

In the spectra of *(1)*, *(2)*, and *(3)* all the protons of the cyclohexyl group can be seen and can be assigned by correlation with their geometric factors because the paramagnetic shift can be related exclusively to the pseudo-contact interaction. The sole exception is the α-proton of *(2)* and *(3)*, whose shift contains a considerable contribution from Fermi contact interactions. The ΔG value for ring inversion of *(1)* can be obtained directly from intensity measurements at low temperatures. Structural information can also be obtained.

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Determination of the Relative Electron Density at the Be Nucleus in Various Chemical Compounds, Measured as the Change in the EC Half Life of ^{7}Be

By *D. C. Aumann* (lecturer), *H. W. Johlige*, and *H.-J. Born*[*]

The change in the EC decay constant of ^{7}Be in various chemical compounds was measured with a differential ionization chamber. The results are

$$\lambda(BeO) - \lambda(BeF_2)_{amorph} = (1.130 \pm 0.058) \times 10^{-3}\lambda(Be)$$
$$\lambda(BeO) - \lambda(Be_4O(CH_3COO_6) = (-0.724 \pm 0.057) \times 10^{-3}\lambda(Be)$$
$$\lambda(BeO) - \lambda(BeBr_2) = (1.472 \pm 0.063) \times 10^{-3}\lambda(Be)$$
$$\lambda(Be_4O(CH_3COO)_6) - \lambda(BeF_2)_{amorph} = (1.852 \pm 0.082) \times 10^{-3}\lambda(Be)$$
$$\lambda(BeO) - \lambda(Be(C_5H_5)_2) = (0.795 \pm 0.074) \times 10^{-3}\lambda(Be)$$
$$\lambda(BeO) - \lambda(Be^{2+}(OH_2)_4) = (-0.374 \pm 0.077) \times 10^{-3}\lambda(Be)$$
$$\lambda(Be(C_5H_5)_2) - \lambda(Be^{2+}(OH_2)_4) = (-1.169 \pm 0.106) \times 10^{-3}\lambda(Be)$$

The decay constant of ^{7}Be is proportional to the electron density at the Be nucleus. These results can therefore be used to construct a scale of relative electron densities at the Be nucleus in various chemical compounds.

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Transformation of Flavonols by an Enzyme from *Cicer arietinum*

By *Wolfgang Barz* (Lecturer) and *Wolfgang Hösel*[*]

By experiments involving pulse labeling we have shown that the flavonols kaempferol, quercetin, and isorhamnetin

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are metabolically active constituents of *Cicer arietinum*. We have now isolated an enzyme preparation that transforms specifically flavonol aglycones in an oxygen-dependent reaction. The very labile product of the enzyme reaction, which can be purified by paper and column chromatography (Sephadex LH 20), consists, according to its UV, IR, and nuclear magnetic resonance spectra, of a flavonoid with a modified γ-pyrone ring. Because of the great similarity of the substance to dihydroflavonols, the electrophoretic and spectroscopic properties, and the ready acid-catalyzed regeneration of flavonols, we conclude that it has the structure of a 2,3-dihydroxyflavanone.

This enzyme, which is so far the only known plant enzyme transforming flavonols, could be shown to be present in a large number of plants. In *C. arietinum* its presence is confined to the root, hypocotyl, cotyledons, and stem.

Possible Reactions in Organic Electrochemistry

By *Fritz Beck*[*]

Electrode reactions of organic molecules X lead primarily to radical ions, which in follow-up reactions with nucleophilic ($\mathcal{N}$) or electrophilic ($\mathcal{E}$) reactants afford the products (P):

Cathodic:

$$X \xrightarrow{\ominus} X.^{\ominus} \xrightarrow{\mathcal{E}} e, c \ldots . P$$

Anodic:

$$X: \xrightarrow{-\ominus} X.^{\oplus} \xrightarrow{\mathcal{N}} e, c \ldots . P$$

Although much information is available from electrochemical measurements about the primary reaction, particularly in aprotic solvents, little is known about the kinetics of the subsequent reactions, *i. e.* the chemistry of the radical ions.

The possible reactions in organic electrochemistry can be divided into two groups:

1. X is not identical with $\mathcal{E}, \mathcal{N}$

These include hydrogenations, oxidations, substitutions, and mixed dimerizations. Elimination reactions can also be assigned to this group.

$\mathcal{E} = H^{\oplus}, CO_2, CO, SO_3, SO_2$;
$\mathcal{N} = Cl^{\ominus}, F^{\ominus}, OH^{\ominus}, OCH_3^{\ominus}, CH_3COO^{\ominus}, NO_2^{\ominus}$, *etc.*

2. X is identical with $\mathcal{E}, \mathcal{N}$

These embrace dimerizations and polymerizations. The mode of reaction is favored by high substrate concentration, high dielectric constant, and shielding of the charge of the radical ion.

A selection of the preparatively and industrially interesting reactions was discussed. Organic electrosynthesis is without competitors above all when the specific conditions at the interface through which the current flows (high, controllable electric field strength, adsorption, concentration profile in the diffusion layer, structure of the electrochemical double layer) are particularly favorable for the desired reaction course. The environmental advantages of electrochemical reactions are also obtaining increasing recognition.

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The Crystal Structure of $EuBr_2$

By *H. P. Beck* (Lecturer) and *H. Bärnighausen*[*]

Using three-dimensional single-crystal X-ray data (Mo-K_α radiation) the crystal structure of $EuBr_2$ has been determined by interpretation of Patterson syntheses and least squares refinement (see Table).

Table. Crystal data, positional parameters, and Debye-Waller factors of $EuBr_2$ (tetragonal; $a = 11.567$, $c = 7.094$ Å; space group P4/n (No 85); $Z = 10$).

Atom	Position	x	y	z	B(Å^2)
Eu(1)	8 (g)	0.1030	0.5871	0.2489	1.52
Eu(2)	2 (c)	0.25	0.25	0.8555	1.39
Br(1)	8 (g)	0.1554	0.4605	0.6256	2.02
Br(2)	8 (g)	0.3390	0.4576	0.1025	1.59
Br(3)	2 (a)	0.25	0.75	0.0	1.38
Br(4)	2 (b)	0.25	0.75	0.5	1.46

In the crystal structure of $EuBr_2$, both Eu(1) and Eu(2) are surrounded by 8 Br^- ions in a square antiprismatic arrangement [however, this idealized geometry is considerably distorted in the case of the cation Eu(1)]. The arrangement of the Eu coordination polyhedra can be compared with that of cubic close packed spheres, so that it is tempting to draw a parallel with the fluorite type. In both structures the cations are eight-fold coordinated, and the geometric arrangements of the coordination polyhedra are also the same. The only difference lies in the geometry of the polyhedra, in that the square antiprism of $EuBr_2$ contrasts with the cubic coordination of the fluorite type.

As expected, $EuBr_2$ and $SrBr_2$ are strictly isostructural. The statistical distribution of the Sr(2) cations over two different positions discussed in the literature as a possibility can now be ruled out conclusively since the original hypothesis can be assigned to faulty interpretation of the powder diagram.

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Photoelectron Spectra of Organometallic Compounds

By *Hans Bock*[*]

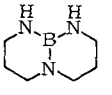
Photoelectron spectroscopy is a molecular probe for σ- and π-interactions, which provides information on the electronic structure of molecules up to now inaccessible.

Topics discussed were:

1. π-systems and geometry of aminoboranes.

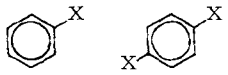
$(R_2N)_nBX_{3-n}$ n = 1,2,3; X = H, CH_3, F, Cl, Br





2. Substituent effects from the perturbation of the benzene π-system.

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X = NR_2, PR_2, OR, SR

3. Acceptor properties of silyl groups towards electron pairs and π-systems.

$X(SiH_3)$, X = Br or OR $\pi(SiH_3)$, π = C_2H_3 or C_6H_5

4. σ-electron delocalization in polysilane chains and rings.

$R(SiR_2)_nR$, n = 1,2,3,4,5 $(SiR_2)_m$, m = 5,6

Coupling Products of Diazotized Anthranilic Acid and *p*-Alkylphenols for Separation, Enrichment, and Determination of Beryllium

By *Ewald Blasius* (Lecturer), *Horst-Joachim Finkenauer*, and *Klaus-Peter Janzen*[*]

o-Hydroxy-*o'*-carboxy-disubstituted azo dyes are selective complexing agents for Be(II).

Coupling products of diazotized anthranilic acid with poly-4-hydroxystyrene or *p*-dodecylphenol are used for separation and enrichment of traces of Be(II) as solid or liquid chelate exchangers, respectively.

o-(2-Hydroxy-5-methylphenylazo)benzoic acid, as a coupling product analogous to that of *p*-cresol, makes possible the synergic extraction of Be(II) from water/methanol mixtures that contain Al(III) and Fe(III).

The Be(II) complex can be detected polarographically to a limiting concentration of 10^{-9} mol/ml in presence of Al(III), Fe(III), Co(II), Ni(II), or Cu(II). The complex can also be determined by inverse voltammetry or photometry at concentrations of, respectively, 10^{-10} mol/ml and 10^{-9} mol/ml.

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Influence of Electrocatalytic Properties of Tungsten Carbide on Anodic Oxidation of Hydrogen

By *Harald Böhm* (Lecturer) and *Wolfgang Diemer*[*]

The anodic oxidation of hydrogen on smooth tungsten carbide electrodes and on rotating tungsten carbide disk electrodes has been studied. The kinetics of the overall reaction were determined by the adsorption of the hydrogen on tungsten carbide. The exchange current density of the hydrogen reaction depends on the mode of preparation of the tungsten carbide; values between 4×10^{-7} and 8×10^{-5} A/cm² were found for i_0. The catalytic activity of the tungsten carbide and thus i_0 are influenced by the carbon and oxygen contents of the sample. Thus the highest activity is found at a carbon content of about 5.9% and not at the content of 6.12% that is calculated for pure WC. The current density of anodic oxidation of hydrogen can be increased by a factor of 2 by partial oxidation of the tungsten carbide surface.

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Preparation and Properties of Oligomeric Polynuclear Phenolic Compounds Containing Nitrophenol Components

By *Volker Böhmer* (Lecturer) and *Hermann Kämmerer*[*]

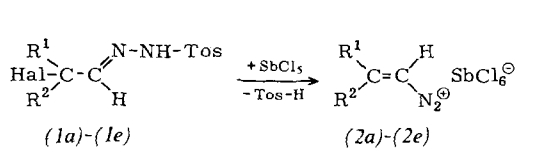
Molecularly homogeneous phenolic polynuclear compounds containing nitro groups cannot be prepared by nitration of preformed polynuclear compounds. Nevertheless, compounds with up to four phenolic units per molecule each carrying at least one nitro group can be prepared either by condensation of nitrophenols with formaldehyde in the presence of sulfuric acid or by condensation of chloromethylated nitrophenols with other nitrophenols in the presence of zinc chloride. On condensation of chloromethylated nitrophenols with methylphenols, however, substitution occurs not only in the *ortho*- but also in the *meta*-position to the phenolic OH group. With binuclear compounds the two isomeric products can be isolated and identified by NMR spectroscopy. New compounds can then be obtained from such "mixed" polynuclear compounds by hydroxymethylation and further condensation. The UV spectra of the oligomers obtained can in some cases be explained over the whole spectral region by addition of "increments" for the individual units.

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Synthesis and Properties of Ethylenediazonium Salts

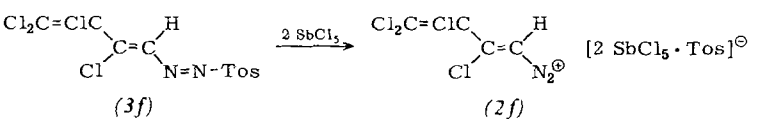
By *Kaspar Bott*[*]

The action of Lewis acids such as antimony pentachloride, aluminum chloride, and stannic tetrachloride on *p*-toluenesulfonylhydrazones *(1a)—(1e)* of α-halogenated aldehydes in chlorohydrocarbons affords, in some cases in high yield, substituted ethylenediazonium salts that, with the exception of *(2d)*, can be isolated as well-crystalline hexachloroantimonates *(2a)—(2e)*. By using *(3f)* and *(3g)* as examples it was shown that the azosulfones postulated as intermediates can be isolated and then converted by antimony pentachloride or a mixture thereof with hydrogen chloride into a diazonium chlorosulfinatoantimonate *(2f)* or hexachloroantimonate *(2g)*, respectively. The compound *(2b)* is also accessible by reaction of nitrosyl hexachloroantimonate with 2,2-dichlorovinyl isocyanate. In all the reactions of ethylenediazonium salts with "basic" reagents the azo coupling is repressed in favor of attack on the β-carbon atom; the particularly reactive *(2b)* substitutes the *p*-hydrogen of anisole even below room tem-



(1a)-(1e) *(2a)-(2e)*

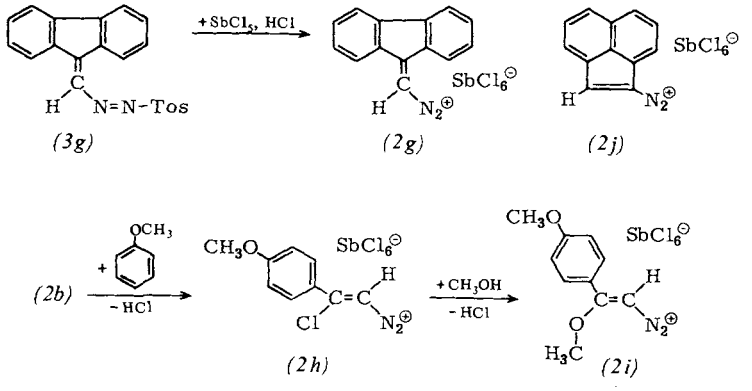
(a), R^1 = H, R^2 = Cl
(b), R^1 = R^2 = Cl
(c), R^1 = Cl, R^2 = tert.-C_4H_9
(d), R^1 = Cl, R^2 = C_2H_5
(e), R^1 = R^2 = Br



(3f) *(2f)*

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perature, but the second halogen atom of the resulting 2-chloro-2-(*p*-methoxyphenyl)ethylenediazonium hexachloroantimonate *(2h)* is replaceable only by the more strongly basic methanol. Finally, an α,β-diaryl-substituted



ethylenediazonium salt was also synthesized, namely, the deep green *(2j)*, which with its reactive double bond and its relatively long-wavelength N≡N stretching band (as a measure of the resonance stabilization) fits well into the series of substances *(2a)*—*(2i)*.

A Contribution to the Mode of Reaction of Anthrahydroquinones with Formaldehyde

By *Karl Bredereck* (Lecturer) and *Lothar Banzhaf*[*]

The mode of reaction of substituted anthrahydroquinones with formaldehyde in aqueous ethanol in the pH region 7—14 has been investigated. Direct-current polarographic measurements showed that anthrahydroquinones that are amenable to enol-keto rearrangement undergo, in the presence of formaldehyde, a reversible equilibration affording 10-hydroxy-10-(hydroxymethyl)-9-anthrones. In individual cases it was possible to isolate these very labile compounds and prove their structure. Further, amino- and hydroxy-anthrahydroquinones and formaldehyde can form ring-methylated anthraquinones; this reaction (the Marschalk reaction) was also studied polarographically; the formation of (hydroxymethyl)anthrahydroquinones as intermediates could be proved.

It was also found that nucleofugal leaving groups in the 2-position of 1-aminoanthraquinones were replaced smoothly by hydroxymethyl or aminomethyl groups on reaction with, respectively, formaldehyde or formaldehyde/amines and sodium dithionite as reducing agent.

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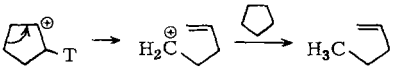
Gaseous Carbonium Ions from the Decay of Tritiated Molecules

By *Fulvio Cacace*[*]

When a T atom covalently bound to carbon undergoes β decay, the daughter ^3He is rapidly lost as a neutral atom, and a carbonium ion is formed[1], *e.g.*:

$$CH_3T \xrightarrow{\text{beta decay}} CH_3^{\oplus} + {}^3He + \beta^- \quad (1)$$

If the original molecule contains at least two radioactive atoms, a *labeled* carbonium ion is formed, whose reactions can be conveniently followed and the final products identified. In recent years, the decay of tritiated precursors has been extensively used as a convenient tool to investigate the stability and the reactions of carbonium ions of precisely defined structure in gases at atmospheric pressure[2]. Among the many systems investigated, a few representative ones are briefly discussed. The $CT_3^{\oplus}$ ions from the decay of CT_4 were shown to react rapidly with CH_4 at 760 torr, yielding ethyl ions that are unreactive towards methane. Both methyl and ethyl ions, on the other hand, readily abstract a hydride ion from higher alkanes to yield, respectively, CT_3H and tritiated ethane. As a whole, these results show a significant analogy with those obtained in $HFSO_3/SbF_5$ solutions[3]. The cyclopentyl cation obtained from the decay of $C_5H_8T_2$ was found to retain its cyclic structure, undergoing rearrangement to the linear pentenyl cation only to a limited extent:



(2)

The decay of molecular tritium yields an exceedingly strong *Brønsted* acid, the helium tritide ion, whose reactions with organic substrates represent another convenient route to gaseous carbonium ions:

$$T_2 \rightarrow {}^3HeT^{\oplus} + \beta^- \quad (3)$$

$$HeT^{\oplus} + RH \rightarrow RHT^{\oplus} + He \quad (4)$$

The tritiation of the appropriate gaseous substrates by the $HeT^{\oplus}$ reagent provided the first direct evidence for the long postulated occurrence of cycloalkanium ions as stable gaseous species. In particular, the intervention of protonated cyclopropanes was unambiguously established by the gas-phase tritiation of cyclopropane and *cis*- and *trans*-dimethyl cyclopropane at pressure of several hundred torr[4]. Reaction (4) proved particularly useful for the study of the gas-phase electrophilic substitutions of aromatic substrates, including benzene, toluene, *tert*-butylbenzene, the halobenzenes, benzonitrile, anisole and α-trifluorotoluene. The contrast between the very low substrate selectivity and the measurable positional selectivity, represents a distinctive feature of the gas-phase reactions, as shown by the study of related gaseous reagents, and suggests that their reaction mechanism must significantly differ from those postulated for the corresponding processes occurring in solution.

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[1] For mass spectrometric studies of these processes see *S. Wexler*: Actions Chimiques et Biochimiques des Radiations. Masson, Paris 1965, Vol. 8, p. 110.

[2] *F. Cacace*, Advan. Phys. Org. Chem. *8*, 79 (1970), and literature cited therein.

[3] *S. A. Olah, G. Klopman*, and *R. H. Schlosberg*, J. Amer. Chem. Soc. *91*, 3261 (1969).

[4] *F. Cacace, A. Guarino*, and *M. Speranza*, J. Amer. Chem. Soc. *93*, 1088 (1971).

Aligned Composites Prepared by Solid State Transformations

By *F. M. A. Carpay*[*]

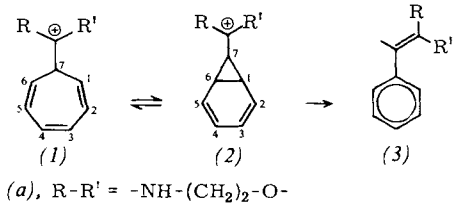
By using the same experimental techniques as in directed eutectic solidification we have effected eutectoidal decomposition and cellular precipitation under directed control. Under unidirectional cooling conditions—for example, by mechanical movement through a temperature gradient—the transformation proceeds in a directed manner. The resulting lamellar structure is illustrated by examples: the eutectoids Co_3Si, β-Cu-In, β-Ni-In, β-Cu-Al, and the separation of Sn in Pb. High rates of movement give undirected structures. The distances between lamellae which occur on discontinuous solid-state transformations are found to be on the average smaller by a factor of 10 than those obtained on directed eutectic solidification with comparable rates of movement. The interlamellar spacings are of the order of 0.1 to 1 μm. Further, the relation between lamellar spacing λ and rate of movement R is not the same as for eutectics; for the eutectoids Co_3Si and β-Ni-In we found experimentally: $\lambda^4 R$ = a constant. This relation was explained in detail.

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Properties and Reactions of Stable 7-Cycloheptatrienyl Carbonium Ions

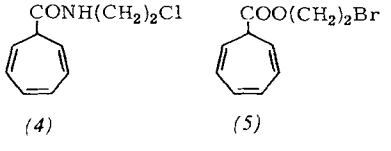
By *Jörg Daub* (Lecturer) and *Werner Betz*[*]

Cations that are stabilized by heteroatoms make it possible to study in greater detail the course of the known rearrangement of intermediate 7-cycloheptatrienyl carbonium ions *(1)* into styrene derivatives *(3)*.



(1) *(2)* *(3)*

(a), R-R' = -NH-$(CH_2)_2$-O-
(b), R-R' = -O-$(CH_2)_2$-O-



(4) *(5)*

Reaction of *(4)* with silver tetrafluoroborate yields *(1a)* for which existence of a dynamic equilibrium between cycloheptatriene and norcaradiene structures has been established by ^{1}H-NMR spectroscopy (temperature-dependence of chemical shifts). Above 100 °C, *(1a)* isomerizes with ring contraction to the benzene derivative. From *(5)* and $AgBr_4$ the benzene derivative is formed directly at room temperature.

These results agree with theoretical considerations: as a stronger electron-acceptor, the positive charge in *(1b)*, gives better stabilization of the norcaradiene structure, thus weakening the bonds between C-7 and C-1, and C-7 and C-6.

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Cyclization of Cyanoethylated Aliphatic Ketones

By *Martin Cherubim* (Lecturer) and *Faisal Abo Dagga*[*]

Ketones containing CH groups in α-position to the carbonyl group can be cyanoethylated in presence of suitable catalysts, yielding mono- or poly-substituted ketone derivatives. 3-Pentanone affords mainly a monocyanoethylated and two dicyanoethylated ketone derivatives, these two being position isomers. Under suitable conditions, one of the position isomers, namely 2,2-bis(2-cyanoethyl)-3-pentanone, is cyclized to 3-amino-6-(2-cyanoethyl)-2,6-dimethyl-2-cyclohexenone. Similar cyclizations were effected also with other cyanoethylated ketones that had free CH_2 or CH_3 groups near the carbonyl group, *e.g.*, with 2-(2-cyanoethyl)-3-pentanone, 3,3-bis(2-cyanoethyl)-2-butanone, and 1,1,1-tris(2-cyanoethyl)-2-propanone. Further, a bicyclic compound was obtained from 3,3-bis(2-cyanoethyl)-2-butanone.

A tautomeric equilibrium exists between the isomers with ketimine and enamine structure. Cyclization of monocyanoethylated ketones and hydrolysis of the enamines affords dihydroresorcinol or derivatives thereof.

3-(4-Hydroxy-1,3-dimethyl-2-oxo-3-cyclohexenyl)propionic acid is obtained by hydrolysis of 3-amino-6-(2-cyanoethyl)-2,6-dimethyl-2-cyclohexenone or analogously by alkali treatment of 2,2-bis(2-cyanoethyl)-3-pentanone. Other cyanoethylated ketones and their cyclization products react similarly.

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Determination of the Molecular Weight Distribution in Nylon 6 by Solution Fractionation

By *Hans Craubner*[*]

The use of a new solution fractionation apparatus for the determination of the molecular weight distribution in nylon 6 was described.

The poly-ε-caprolactam was fractionated by extraction with solvents of increasing solvent strengths, including concentrated formic acid, between 20 and 90 °C. The molecular weight distribution was determined from the weight fractions and the viscometric molecular weights. The number average and the weight average molecular weights of the sample as a whole are $\bar{M}_n = 14800$ and $\bar{M}_w = 24600$. The nonuniformity is $U = (\bar{M}_w/\bar{M}_n) - 1 = 0.66$.

The statistical analysis shows a three-component mixed distribution. This is explained by the preparation of the polymer (polymerization, granulation, extraction with hot water, drying). The linear nylon 6 with an extremely narrow distribution accounts for more than 98 wt. %. It is preceded by a small oligomer fraction (<1%). The tail of the distribution is formed by a small high molecular weight component consisting of weakly crosslinked material

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(<1%). The mean properties calculated from the distribution, such as, for example, the intrinsic viscosity ($[\eta] = 104\ cm^3/g$), agree quantitatively with the measurements on the starting material.

The narrow nylon 6 distribution found by solution fractionation is confirmed by fast turbidimetric titration according to dynamic volume pulse techniques.

Charge Distribution in the Chain 132 from the Fission of Uranium-235 and Uranium-233 by Thermal Neutrons

By *H. O. Denschlag* (Lecturer), *R. Naeumann*, and *H. Folger*[*]

The fractional independent and cumulative fission yields of the three principal chain members of mass 132—tin, antimony, and tellurium—obtained from the fission of U-235 and U-233 by thermal neutrons have been measured. For this purpose the elements concerned were rapidly separated from one another as hydrides. The following yields (in percentages) were found for the fission of U-235 [U-233]:

Sn-132: 13.7 ± 0.8 [2.5 ± 0.5] (cumulative),
Sb-132: 48.7 ± 1.0 [27.1 ± 3.0] (independent), and
Te-132: 37.6 ± 1.5 [64.4 ± 4.0] (independent)

These afford the following Z_p values for the two fission reactions:

$$51.28\ ^{+\ 0.10}_{-\ 0.30}\left[51.75\ ^{+\ 0.10}_{-\ 0.15}\right]$$

The deviation of the most probable nuclear charge in the chain 132 from the value calculated with the assumption that the charge density is unchanged from that of the compound nucleus follows with $\Delta Z = -0.37^{+0.10}_{-0.30}$ for the fission of U-235 and $\Delta Z = -0.34^{+0.10}_{-0.15}$ for the fission of U-233. No local effect of the closed shells of 50 protons and 82 neutrons in $^{132}_{50}Sn^{82}$ on the charge distribution was observed.

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[**] On leave from the Institute of Inorganic Chemistry, University of Trondheim-NTH, Norway, recipient of a Grant from the Royal Norwegian Council for Scientific and Industrial Research.

Gel Adsorption Chromatography

By *Helmut Determann* (Lecturer) and *Klaus Lampert*[*]

The retardation of dissolved (mostly low-molecular) substances by interaction with a gel matrix was originally regarded as a source of interference in normal gel-chromatographic separation. Meanwhile it has been shown in various schools that very effective separations can be achieved by using selective retardation, outside the gel filtration scheme. The effects may be caused by van der Waals forces, hydrogen bonding, and hydrophobic interaction, whose influences naturally overlap. Nevertheless the contributions of, in particular, hydrogen bonding and hydrophobic interaction can largely be studied separately by variation of the test substances, gel materials, solvent, and temperature. It is now possible, given a knowledge of the rules of gel adsorption chromatography, to define conditions that will afford optimal separation in actual cases.

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Solvolysis of Polyepoxides of Unbranched Polybutadienes

By *Walter Dittmann* (Lecturer) and *Karl Hamann*[*]

An anomaly is found in the mode of reaction of linear polybutadiene epoxides with ring-cleaving agents such as water, methanol, or hydrogen chloride. By the application of statistical methods to the experimental findings, it has been shown that sequences of epoxide groups in a 1,5 position with respect to one another react by addition of the solvolytic agent across the "ends", with intramolecular ether formation within the sequences. This anomalous reaction explains why the epoxide values found by chemical methods are too low. It agrees with the conformation proposed for unbranched polybutadienes on the basis of the UV spectrum, and rules out the indirect formation of head-to-head polymers, *e.g.* head-to-head polyvinyl alcohol, by hydrolysis of polybutadiene epoxides.

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Investigation of the Furnace Black Process in a Model Reactor

By *Gerhard Kühner* and *Gunther Dittrich* (Lecturer)[*]

Experiments with a pilot-scale furnace carbon black plant are described that enable the observed relations between yield of carbon black and throughputs of raw materials (benzene; illuminating gas as heating gas; air) to be interpreted quantitatively. For this purpose the furnace black reaction

$$a C_6H_6 + b O_2 + 4b N_2 \rightarrow 4b N_2 + c C_{black} + d CO + e CO_2 + f H_2O + g H_2$$

is broken down into cleavage and various possible combustion reactions, *e.g.*:

$$C_6H_6 + 0.0\ O_2 \rightarrow 6\ C + 3\ H_2;$$
$$\cdots$$
$$C_6H_6 + 1.5\ O_2 \rightarrow 6\ C + 3\ H_2O;$$
$$\cdots$$
$$C_6H_6 + 6\ O_2 \rightleftharpoons 6\ CO_2 + 3\ H_2;$$
$$\cdots$$

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By linear combination of the equations the yield of carbon black is obtained as

$$A = 100 - \frac{V \times 100}{6} \times \frac{S}{B}(\%)$$

S and B are the amounts of oxygen and benzene, respectively, in mol, and V is a factor that depends on S and the positions of the Boudouard and water-gas equilibria.

A similar equation is obtained for the presence of heating gas. Further, relations are derived between the exit gas composition and the yield of black and between the mean reactor temperature and the molar ratio benzene/air.

Preparation of Multicomponent Oxide Glasses by Polycondensation

By *Helmut Dislich*[*]

Alcoholates of different metals react with one another to give alkoxo complexes that can be converted into homogeneous multicomponent oxides by hydrolysis and polycondensation reactions involving loss of alcohol and water. Multicomponent oxide glasses can thus be obtained without passage through a molten phase.

Thus glass—the "oldest thermoplast"—is accessible by a route that is customary in macromolecular chemistry and in particular in organosilicon chemistry. The method is suitable especially for preparation of thin layers on substrates to withstand a temperature around 500 °C. Several of these layers delay the flaking of iron and the tarnishing and corrosion of brass and protect sensitive glasses from climatic effects.

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The Influence of Apparative Gas-Chromatographic Parameters on the Detector Response of Thermocouple Detectors

By *H. W. Dürbeck*[*]

To obtain reproducible results with standard deviations of about 1% in quantitative gas-chromatographic analysis with thermocouple detectors it is necessary to have a fundamental knowledge of the influencing effects caused by systematic or occasional changes of apparative parameters, *i.e.* bridge current, type of carrier gas and its rate of flow, oven temperature and block temperature of the thermocouple detector.

The following are the principal results of investigations carried out in a systematic study.

1. The stability of bridge current and carrier gas velocity is of fundamental importance.
2. Changes in block temperature of the thermocouple detector are less important but depend on the nature of sample or carrier gas as regards the mathematical sign.
3. The oven temperature of the gas chromatograph usually has no effect.
4. The nature of the carrier gas mainly influences the sensitivity and dynamic behavior of the thermocouple detector.

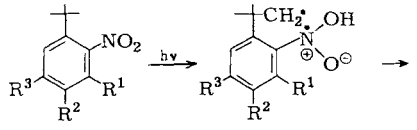
Quantitative correlations were given.

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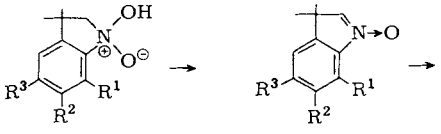
Photoreactions of Sterically Hindered Nitro Compounds. Light-Induced Formation of Nitrones from *o-tert*-Butylnitrobenzenes

By *Dietrich Döpp* (Lecturer), *Karl-Heinz Sailer*, and *Erhard Brugger*[*]

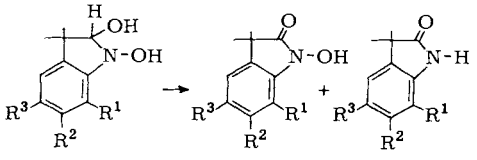
When *(1a)*, *(1b)* are irradiated as crystalline powders with simulated sunlight and the crude photolyzate is chromatographed on silica gel, compounds *(4a)*, *(4b)*, *(6a)*, *(6b)*, *(7a)*, *(7b)*, and *(8)* are obtained, as well as by-products which, like *(6a)*, *(6b)*, *(7a)*, *(7b)*, and *(8)*, are obtained from *(4a)*, *(4b)* by way of their hydrates *(5a)*, *(5b)*. The *N*-formyl group in *(8)* is derived from one methyl group of that side chain of *(1a)* which is in *ortho*-position to the NO_2 group.



(1a), (1b) *(2a), (2b)*



(3a), (3b) *(4a), (4b)*

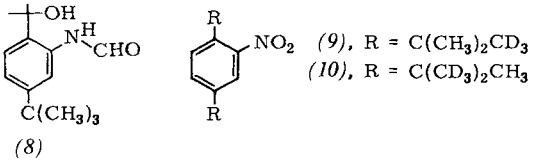


(5a), (5b) *(6a), (6b)* *(7a), (7b)*

(a), $R^1 = R^3 = H$, $R^2 = C(CH_3)_3$;
(b), $R^1 = R^3 = C(CH_3)_3$, $R^2 = H$

The conversion of *(1)* into *(4)* begins with an intramolecular abstraction of a hydrogen atom from the β-position of the side chain by the excited nitro group *via* a seven-membered transition state to *(2)* which affords *(4)* *via (3)* by loss of water from the latter.

When the crystalline compounds *(9)* and *(10)* that are more than 99% deuterated in the positions shown are irradiated, an isotope effect $k_H/k_D \approx 3.9$ is found; on irradiation in methanol solution, however, the k_H/k_D ratio is 4.4.



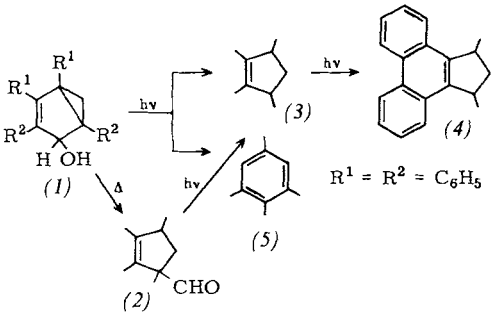
(8) *(9)*, R = $C(CH_3)_2CD_3$
(10), R = $C(CD_3)_2CH_3$

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Bicyclohexenols as Benzvalene Derivatives, and Their Photochemical Reactions

By *Heinz Dürr* (Lecturer), *Peter Heitkämper*, and *Peter Herbst*[*]

On irradiation by Hg high-pressure lamps, tetrasubstituted *exo*- and *endo*-bicyclo[3.1.0]hex-3-enols *(1)* undergo a stereospecific reaction that gives good yields of tetrasubstituted cyclopentenes *(3)* together with phenanthrene *(4)* and benzene derivatives *(5)* as by-products. Thermolysis of *(1)* affords β,γ-unsaturated cyclopentenecarbaldehydes *(2)*, which also fragment to *(3)*. Further, *(2)* can be shown to be intermediate in the photolysis of *(1)*. The intramolecular course of the photoreaction was demonstrated by isotopic labeling (deuterium). The multiplicity of individual steps was clarified by sensitization studies, and the quantum yields were determined by use of radioactive isotopes (tritium). The reaction mechanism of the photoreactions thus determined was discussed.

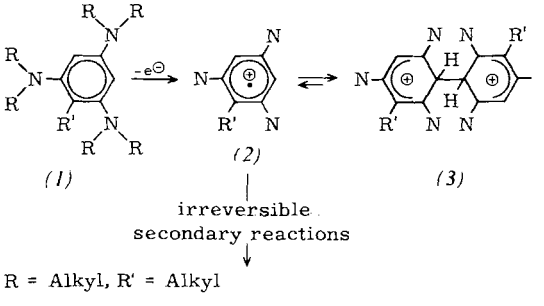


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Oxidative Dimerization of Aminobenzenes

By *Franz Effenberger* (Lecturer), *Klaus Nagel*, and *Gerhard Epple*[*]

Preparative and kinetic findings prove the reaction sequence *(1)*→*(2)*→*(3)* for the oxidation of 1,3,5-triaminobenzenes *(1)*. *(2)* and *(3)* are in rapid equilibrium, from which *(2)* may be removed irreversibly by secondary reactions, *e.g.*, with the solvent.



On the basis of UV and NMR spectra the conformations of differently substituted dimers *(3)* were discussed. Intramolecular interaction between the two phenonium rings of *(3)* must be concluded from the spectra and from calculations.

The mechanistic concept developed for triaminobenzenes can be extended to the oxidation of anilines. The bromination of *N,N*-dialkylanilines, involving nuclear bromination, dealkylation, and oxidation, was discussed in detail.

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Determination of the Distribution of Radii of Polymer Dispersions on Macroporous Silica Gels

By *Winfried Wunderlich*, *Karl-Friedrich Krebs*, and *Friedhelm Eisenbeiss* (Lecturer)[*]

The carriers required for gel-chromatographic separation of particles such as dispersed polymers, cell constituents, viruses, and the like must have extremely large pores corresponding to the size of the particles to be separated and they must be mechanically stable. We have prepared such materials, on the basis of silica gels, with pore diameters up to 25000 Å and with a narrow distribution of pore size[1].

Several polymer dispersions whose mean particle radius was determined by electron microscopy and light scattering measurements to be between 150 and 2500 Å were placed on such silica gels, and the elution volumes of the bands were measured.

Plotting the mean particle radii against the corresponding elution volumes gave relations such as can be found in gel permeation chromatography of polymers (log M against V_e). In this way the mean radii and particle size distribution of "unknown" dispersions can be determined from gel-chromatographic data for the system. The experiments were carried out in the apparatus customarily used for gel chromatography.

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[1] German and other patents applied for by the E. Merck company.

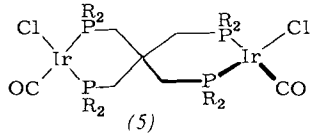
Carbonylhalogenohydrido-, Carbonylhalogeno-, and Halogeno-iridium Complexes Involving a Tetradentate Phosphane

By *Jochen Ellermann* (Lecturer), *Rainer Gerbeth*[*], and *Kurt Geibel*[**]

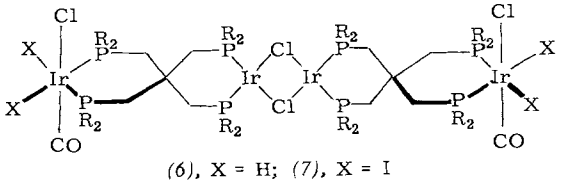
The square planar *trans*-iridium(I) complex $[Ir\langle(CO)Cl\rangle\langle(PR_3)_2\rangle]$ $(R = C_6H_5)$ *(1)* is formed in the system $PR_3/IrCl_3(H_2O)_3$ *(2)* in presence of $CH_3O(CH_2)_2O(CH_2)_2OH$ *(3)* as solvent and carbonylating and reducing agent[1]. It is of interest as a model for biochemical O_2 fixation. This fixation is irreversible if the Cl is replaced by I. It is not yet known whether iridium(I) complexes analogous to *(1)* but with *cis*-organophosphorus groups exist and whether they also fix oxygen.

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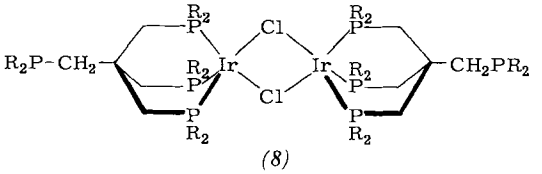
If *(2)* (2 mol) is treated with $C(CH_2PR_2)_4$ ($R=C_6H_5$) *(4)* (1 mol), which because of its geminal system can react as a bidentate ligand only with *cis*-coordination, the expected spirocyclic complex *(5)* is not obtained but instead the hydrido complex *(6)* [^{1}H-NMR: $\tau=20.1$ ppm, $^2J_{trans H,P}=$ 100 Hz (doublet), proof by spin decoupling of ^{31}P; IR: ν(CO) and ν(IrH) = 2055, 1973 sh, 1965, δ(IrH) = 795, 781 cm^{-1}]. With CH_3I, *(6)* forms the iodo complex *(7)* [IR: ν(CO) = 2055 cm^{-1}] with elimination of CH_4.



(5)



(6), X = H; *(7)*, X = I



(8)

When a 1:1 molar ratio is used under the same conditions, *(2)* and *(4)* yield *(8)*, which is methylated by CH_3I on both terminal PR_2 groups.

These experiments show that the reactions undergone by iridium are completely changed by two *cis*-coordinated phosphane groups. O_2-fixing iridium complexes with such coordination are thus not immediately accessible.

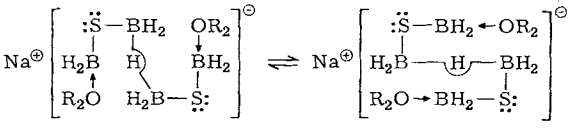
[1] *L. Vaska* and *J. W. DiLuzio*, J. Amer. Chem. Soc. *83*, 2784 (1961).

[2] *J. Ellermann* and *K. Dorn*, Chem. Ber. *101*, 643 (1968).

Cleavage of Diborane(6) by Alkali Metal Sulfides and Polysulfides

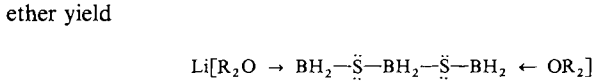
By *Hans-Herbert Friese* and *Udo Engelhardt* (Lecturer)[*]

Diborane(6) and sodium sulfide in tetrahydrofuran at room temperature react with unsymmetrical cleavage to sodium tetrahydridoborate and a compound of composition $Na[B_4H_9S_2\cdot 2R_2O]$, whose method of formation, molecular weight, ^{11}B-NMR spectrum, and IR data indicate a tautomeric structure in solution:



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Use of an anhydrous sulfide of higher sulfur content, *e.g.*, potassium tetrasulfide, leads to evolution of hydrogen and formation of the above products together with glassy polymers or oligomers of composition $[S(BH_2)_2\cdot xR_2O]_n$. Elemental sulfur does not react with diborane(6) even under more drastic conditions, but octasulfur and lithium tetrahydridoborate afford, besides lithium sulfide, salts of varying composition which with diborane(6) in diethyl ether yield



as main product.

Kinetics and Mechanism of the Degradation of Vinyl Polymers in the Solid State

By *D. H. Everett*[*]

This paper is concerned with a study of the kinetics and mechanism of thermal decomposition of polyvinylidene chloride and its co-polymer (Saran) with polyvinyl chloride in the solid state. The work reported is aimed at elucidating the mechanism by which hydrogen chloride is formed, and the changes which take place in the internal structure of the polymers during degradation. It is found that the rate of decomposition, besides being dependent on temperature, is markedly influenced by pre-irradiation with UV or γ-rays and by the chemical nature of the gas phase in which it is in contact. The kinetics are also influenced by morphological factors. Possible mechanisms for the decomposition process are discussed and related to the observed kinetics. The physical properties of the carbon which results from the decomposition are strongly dependent on the conditions under which the degradation occurs, and an attempt is made to correlate various factors which influence the carbon structure.

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Migration of Additives from Plastic Films into Edible Fats and Fat Simulants

By *Karl Figge*[*]

In order to assess the toxicological harmlessness of plastic packagings used for storing edible fats, the migration of ^{14}C-labeled additives from packaging films into fats or fat simulants was investigated. The additives used were di-*n*-hexyl [1-^{14}C]di-*n*-octyltin bis(2-ethylthioglycolate), [^{14}C]-1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-2,4,6-trimethyl benzene (Ionox-330-^{14}C), [1-^{14}C]stearamide or [1-^{14}C]-*n*-butyl stearate.

The films used were of rigid polyvinyl chloride (PVC), polystyrene (PS), high-density polyethylene (HD-PE), and low-density polyethylene (LD-PE).

Results to date: The passage of an additive from a plastic film into various edible fats such as 'Biskin' (a partially hardened ground-nut oil product), margarine, butter, sunflower oil, and olive oil is similar, but passage from different types of plastic films into an edible fat varies widely.

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The substances shown in Table 1 are suitable as fat simulants.

Table 1. Fat simulants.

Type of plastics	Under conditions of migration (20 °C/60 d)	extraction (65 °C/5 h)
HD- and LD-PE	MCT [a]	—
PS	MCT, paraffin oil, methanol	coconut fat
PVC	tricaprin, HCFA-T [b]	paraffin oil, *n*-heptane

[a] Mixture of medium-chain triglycerides.
[b] Mixture of hydrogenated, cyclic fatty acid triglycerides.

The PVC simulants listed in Table 1, under extraction, give values which are too high for both types of polyethylene. The same is valid for *n*-heptane in the case of PS and for diethyl ether in the case of all four plastics respectively. The amounts of ^{14}C-labeled additive that migrated into triglycerides, and the increase in weight of the films tested, pass through a maximum when plotted against the length of the acyl group; this maximum being particularly steep for PVC and PS.

On the basis of these results a fat simulant has been prepared that contains triglycerides with acyl groups of various lengths. This mixture is suitable as standard fat for all types of plastics, as is shown, *e.g.*, by the comparative migration values of two additives from PS into edible fat and into the fat simulant (Table 2).

Table 2. Comparison of the migration of additives from PS into edible fats and the fat simulant.

Additive	Amount (%) of migrated additive 'Biskin'	butter	coconut fat	fat simulant
Ionox-330-^{14}C	2.1	3.1	2.5	3.1
[1-^{14}C]-Stearamide	5.2	7.1	5.6	7.6

Carbonylrhodium-Tertiary Amine Complexes as Catalysts for the Hydroformylation Reaction

By *Bernhard Fell* (lecturer), *Antoin Geurts*, and *Edwin Müller*[*]

In studies on the Reppe alcohol synthesis from olefins, carbon monoxide, and water with catalysis by carbonyliron-tertiary amine complexes, it was found that this reaction can be extremely favorably influenced by very small quantities of cocatalytically active rhodium compounds. The successful application of the synthesis to olefins having higher molecular weights becomes possible only with this rhodium-modified catalyst system. The results with the Reppe alcohol synthesis led to further systematic experiments with carbonylrhodium-tertiary amine complex catalysts in the hydroformylation and other reactions of olefins. Thus with hydridocarbonyltris(tribenzylamine)-rhodium(I) as the catalyst, just as with the corresponding carbonylrhodium-tertiary phosphane complexes described by *Wilkinson et al.*, the hydroformylation of an olefin can be achieved at a water gas pressure of 1 atm and at normal temperature. With other carbonylrhodium-tertiary amine complexes, a direct one-step oxoalcohol synthesis is possible even at 70—80 °C. After exposure to hydrogen gas for one hour and addition of 5 wt.-% tribenzylamine *N*-oxide a solution of the hydridocarbonyltris(tribenzylamine)rhodium(I) in benzene becomes an active catalyst for the selective isomerization of 1-olefins to the 2-isomers.

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Reactions of Trichloromethyl Isocyanide Dichloride

By *Kurt Findeisen*[*]

Trichloromethyl isocyanide dichloride is synthesized by chlorination of dimethylcarbamoyl chloride. Reactions in which a hydroxyl group or a carbonyl or anhydride oxygen atom is replaced by halogen can often be effected better with trichloromethyl isocyanide dichloride than with thionyl chloride, phosphorus pentachloride, *etc.* The compound can often find use in place of the usual dehydrating reagents.

Trichloromethyl isocyanide dichloride is an interesting component for synthesis of heterocycles: the structural unit Cl—C—N=C—Cl remains intact in formation of *s*-triazines, 1,2,4-triazoles, 2,4,6-trichloropyrimidines, 2,4-dichloroquinazolines, and 1,2,4-oxadiazoles.

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The Existence of 3-Bromo-L-tyrosine in Blood Serum

By *Günter Firnau* (Lecturer) and *Klaus Fritze*[*]

The binding of bromine to the serum proteins of blood[1–3] was investigated. By a tracer study, using ^{82}Br, it is demonstrated that bromine is bound to serum proteins *in vivo*. $K^{82}Br$ of high specific activity (7.5 mg, 40 mCi) was injected into rabbits and serum removed one day later. Approximately 0.5% of the total ^{82}Br in the serum was found to be protein-bound at this stage. The application of various separation methods (electrophoresis, bromide exchange, denaturation followed by desalting on a gel column) showed that one-third of the protein-bound bromine is loosely attached whereas two-thirds are firmly bound.

To elucidate the nature of this firmly bound bromine the serum proteins were completely hydrolyzed[4] and the amino acids were separated on a Dowex-50-X8 column[5]. The radioactivity eluted from the column was associated with 3-bromo-L-tyrosine. No bromine could be detected in thyroxine.

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[1] *H. Doering*, Biochem. Z. *296*, 53 (1938).
[2] *H. Sklavenitis* and *D. Comar*, IAEA Symposium on Nuclear Activation Techniques in Life Science, paper SM 91/45, 1967.
[3] *K. Fritze* and *R. Robertson*, J. Radioanalyt. Chem. *1*, 463 (1968).
[4] *R. L. Hill* and *W. R. Schmidt*, J. Biol. Chem. *237*, 389 (1961).
[5] *S. Moore* and *W. H. Stein*, J. Biol. Chem. *192*, 663 (1951).

Neutron Spectra in the Decay of Some Fission Products

By *H. Franz* (Lecturer), *J.-V. Kratz*, and *Günter Herrmann*[*]

The spectra of delayed neutrons in the thermal neutron induced fission of ^{235}U were measured with a ^{3}He-spectrometer up to energies of 1.5 MeV. In the spectra of the unseparated fission products a number of neutron peaks could be observed. Some of these peaks can be directly assigned to 55-s ^{87}Br because of their half-life. The other peaks are attributed to 24-s ^{137}I and/or 16-s ^{88}Br.

By a rapid chemical separation, arsenic was isolated from the fission products as a volatile hydride. The neutron spectrum of the delayed-neutron precursor 2.05-s ^{85}As was measured. Four prominent neutron peaks could be observed besides some weaker lines. In addition, γ-spectra of the arsenic isotopes were measured with a Ge(Li)-diode. A 2-s component in the decay-curves of the 1455.1 keV and 667.1 keV γ-lines of the 5.4-s ^{84}As proves that excited levels of ^{84}Se are fed by the delayed neutron emission of ^{85}As.

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Mössbauer Effect Measurements on Neptunium Compounds

By *Klaus Fröhlich* (Lecturer), *Philipp Gütlich*, and *Cornelius Keller*[*]

By means of the Mössbauer effect it has been proved that neptunium has the oxidation state +7 in the following compounds: Li_5NpO_6, $[Co(en)_3]NpO_5 \cdot xH_2O$, $Ba_3(NpO_5)_2 \cdot xH_2O$, and $Ca_3(NpO_5)_2 \cdot xH_2O$.

Radiolysis effects were studied for Li_5NpO_6, but no decomposition was oberved after storage of the compound for several months. Mössbauer measurements indicate conclusively that Li_5NpO_6 does not have O_h symmetry, but that the $[NpO_6]^{5-}$ ion is compressed, presumably in the z-direction (neptunyl group) and rhombically distorted in the xy plane.

The neptunium-containing anion of the other compounds studied presumably contains a tetragonal-bipyramidal configuration with the neptunyl group oriented in the z-direction and two oxygen atoms as well as two OH-groups, both in *trans* position, in the xy plane. The neptunyl group is more pronounced than in Li_5NpO_6.

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Kinetics and Mechanism of the Specific Binding of Ions by Cyclodepsipeptide Antibiotics

By *Theodor Funck*, *Frieder Eggers*, and *Ernst Grell* (Lecturer)[*]

Studies on specific complex formation of alkali-metal ions with cyclodepsipeptides such as valinomycin and enniatin B in homogeneous solution are important for the understanding of selective transport of cations through membranes mediated by these antibiotics.

Thermodynamic data were determined for the cation complexes in methanol. The remarkable differences in the stabilities of the various cation complexes can be correlated with the ligand conformation in the complexes as characterized by spectroscopic techniques. Kinetic studies by relaxation methods led to the elucidation of the reaction mechanism. Complexation of cations is due to a multistep reaction, the rate of complexation being remarkably slow and corresponding to the rate of the slowest conformational change of the uncomplexed antibiotic. Differences in the rates of complex formation of the antibiotics with different cations are significant for the mechanism of ion selectivity.

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Preparation and Spectroscopic and Magnetic Investigations of Inorganic Complex Azides

By *Harald P. Fritzer* (Lecturer), *Karl Torkar*, and *Fritz Lunzer*[*]

Complex azides have been prepared in crystalline form from potassium azide, cesium azide, and transition-metal hydroxides or carbonates of zinc, nickel, and cobalt. Analytical investigations yielded the formulas $K_2Zn(N_3)_4$, $Cs_2Zn(N_3)_4$, $K_4Ni(N_3)_6$, and $KCo(N_3)_3$. The Co compound is highly explosive and must be handled with extreme care! The compounds deflagrate strongly in a flame and some are sensitive to shock.

Both electronic diffuse reflection spectra and the magnetic susceptibilities[1] were analyzed by the model of the extended crystal field theory. The aims of these investigations which will be extended also to other complex azides are the determination of the microsymmetry of the transition-metal ion in each azide lattice, determination of optical and magnetic parameters, and, with the aid of some intrinsic properties of the N_3^- ion, characterization of covalent contributions to the metal-ion/azide bond[2].

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[1] At ambient and low-temperature, resp.

[2] The results are discussed in relation to the easy polarizability of the linear π-electron system of N_3^-, yielding large values for the crystal field parameter Δ but low nephelauxetic ratios.

Conformational Analysis and Kinetics of the Conformational Rearrangements of Cyclodepsipeptide Antibiotics

By *Ernst Grell*, *Frieder Eggers*, and *Theodor Funck* (Lecturer)[*]

Conformational transitions of membrane-active antibiotics such as valinomycin and enniatin B have been studied as a function of solvent polarity by ultrasonic absorption measurements. The results provide information about the number of occupied conformational states as well as the rates of interconversion between conformers.

Even in solvents of low polarity at least three conformational states have to be considered for both depsipeptides. The interpretation of the results is confirmed by spectroscopic

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studies. For valinomycin and enniatin B the kinetic measurements show, in addition to relatively rapid processes in the frequency range of 10—100 MHz, slower conformational transitions which are closely related to conformational rearrangements of these ligands during complex formation with cations. The observed conformational changes of valinomycin are due to a stepwise opening of a structure that is stabilized by intramolecular hydrogen bonds whereas the conformational changes of enniatin B are induced by specific solvent effects.

Analysis of Mixtures of Metallic Nickel and Oxide Hydrates of Bivalent and Higher-Valency Nickel

By *Werner Gann*[*]

The quantitative determination of metallic nickel and the effective valency of the nickel present as hydroxides or oxide hydrates in various valency stages in samples moistened with alkali obtained from positive electrodes of alkaline accumulators presents difficulties, since higher-valency Ni compounds decompose spontaneously, and the system does not consist of phases thermodynamically coexistent.

Taking these facts into account, it is possible to find the effective valency to within ± 0.02 valency units and also to determine the metallic component in samples of 50 to 200 mg by the following scheme:

Reduction of the sample, which has been dried with Na_2CO_3 and ground in a mortar, with a large excess of arsenate(III) solution, filtration and reaction of As(V) (formed in an equivalent quantity) with KI setting free elementary, photometrically determinable iodine, extraction of the Ni compounds present in the residue with dilute H_2SO_4, dissolution of the remaining metallic Ni in $H_2SO_4+H_2O_2$, and photometric determination of the Ni solutions as EDTA complex. The results agreed well with those obtained electrochemically.

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Study of the Sorption Behavior of Fruit Powders with a New Type of Automatic Apparatus

By *Heinrich Drexler* and *Karlheinz Gierschner* (Lecturer)[*]

Determination of their sorption isotherms is important for evaluation of fruit powders and other dry foods. Most methods of determining sorption isotherms require a long time, which may result in spoiling of the samples and thus uselessness of the result. Often only a few points of the sorption isotherms can be measured, so that the exact course of the curve cannot be decided.

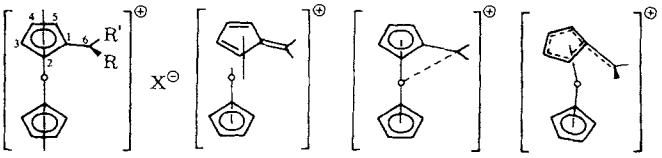
In work with fruit powder a method has been developed for automatic determination of the sorption isotherms. By a special arrangement the vapor pressure (the relative humidity) in the sorption space is altered as soon as the weight of the sample has remained constant for a definite time. With this apparatus as many points as desired on the sorption isotherm can be determined over a large temperature range within 2—3 days.

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Structure of the Ferrocenylmethyl Cation[1]

By *Rolf Gleiter* (Lecturer) and *Rolf Seeger*[*]

Ferrocenylmethyl cations *(1)* can be isolated as stable salts. Their especial stability has been explained either by conjugation with the π system *(2)* or by metal participation *(3)*[2]. The geometry of *(1)* has been varied by an iterative Extended Hückel procedure (S.C.C.) until a state of minimal energy was reached. In the resulting structure *(4)* all the Fe—C overlap populations are about the same.



(1) *(2)* *(3)* *(4)*

This structure arises to a first approximation by interaction of the occupied $3d_{z^2}$ orbital of the iron with the empty π^* orbital of the fulvene moiety.

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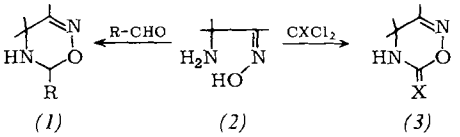
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[2] *M. Cais*, Record Chem. Progr. *27*, 177 (1966), and further literature cited there.

Synthesis of Heterocycles from *syn*- and *anti*-Aminooximes

By *Horst Gnichtel*[*]

Reaction at the amino group of *syn*- and *anti*-α-aminooximes led to electrophilic groups as intermediates whence 1,2,5-oxadiazine derivatives were obtained by reaction of the hydroxyl-oxygen atom of a *syn*-oxime group, and imidazoline *N*-oxides by reaction at the oxime-nitrogen of an *anti*-oxime group.

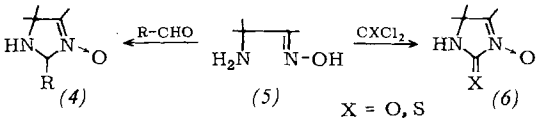
syn-α-Aminooximes *(2)* with aliphatic aldehydes afford 5,6-dihydro-4*H*-1,2,5-oxadiazines *(1)*, and with phosgene or thiophosgene respectively 5,6-dihydro-6-oxo- and 5,6-dihydro-6-thioxo-4*H*-1,2,5-oxadiazines *(3)*, whose structures were proved by spectroscopic data and chemical reactions.



(1) *(2)* *(3)*

X = O, S

anti-α-Aminooximes *(5)* with aldehydes afford 3-imidazoline 3-oxides *(4)* and with phosgene and thiophosgene respectively the 2-oxo and 2-thiooxo derivatives *(6)*. The



(4) *(5)* *(6)*

X = O, S

nitrone structures were proved by 1,3-dipolar addition and spectroscopic data.

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Experiments on the Halogenation of 1,3-Dibromo-1,3-dimethylcyclobutane

By *Karl Griesbaum* (Lecturer), *Mahmud El Borai*, and *Yingli Chu*[*]

The title compound is readily obtained from allene and/or methylacetylene and HBr, and the objective of these experiments was its selective chlorination to afford 1,3-dibromo-2,4-dichloro-1,3-dimethylcyclobutane. Treatment with chlorine or *tert*-butyl hypochlorite gave, however, monochlorides (1,2-dibromo-3-chloro-1,3-dimethylcyclobutanes) in which the entering chlorine substituent replaced one of the bromine atoms already present in the starting material while the bromine atom appeared at one of the previously unsubstituted methylene groups. The migration of the bromine substituent was accompanied by substantial inversion at the tertiary C atom at which the chlorine-bromine exchange occurred.

The structures of the resulting stereoisomeric monochlorides—in particular the position of the chlorine substituents in the molecule—were established in independent syntheses by addition of bromine to 1-chloro-1,3-dimethylcyclobutene. The stereochemical result of this chlorination is indicative of a concerted reaction course, possibly *via* bridged radical intermediates.

Bromination of the title compound also proceeded with partial, but distinctly less, inversion at one of the tertiary C atoms and yielded two isomeric 1,2,3-tribromo-1,3-dimethylcyclobutanes.

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Influence of Microorganisms on the Oxidative Deterioration of Fats

By *Werner Grosch* (Lecturer), *Friedrich Senser*, and *Klaus Fischer*[*]

36 Psychrophilic strains of microorganism that metabolize linoleic acid were isolated from fresh herrings. A preliminary experiment (growth on sunflower oil emulsion) showed that: None of these strains had prooxidative action, but a number of them delayed the autoxidation. Eleven of the latter were cultivated on linoleic acid hydroperoxides (LOOH). Two (F 25 and 29) degraded the hydroperoxy group rapidly and the diene system slowly; the other eight (including F 75) reacted only slowly with LOOH. F 29 can consume LOOH, primarily reducing the 13- and 9-hydroperoxy acid to the hydroxy acid. F 75 (*Pseudomonas fluorescens* sp.), however, reduces the hydroperoxy group more slowly, giving the hydroxy acids which it then consumes; but unlike F 29 it does not multiply in the process.

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Analytical Determination of Phase Equilibration Behavior of Multicomponent Systems in Distillation Columns

By *Helmut Günzler*[*]

Several graphical and algebraic methods of calculation have been described for determination of the number of theoretical plates n_t required for a given distillation operation. The McCabe-Thiele method, which is very simple to use for two-component mixtures, is most often employed, but all the graphical methods fail for mixtures of more than three components. With highly sophisticated programs for large electronic computers it is now possible to handle also very complex mixtures with a close approximation to reality.

All reliable methods of calculation require preknowledge of all the binary phase equilibrium relations of the components of the mixture. Approximate procedures require a knowledge of at least the vapor pressure curves.

In practice it is often the case that not all the equilibrium relations are known or even that the identity of individual materials is uncertain, and this is often the cause for deviation of the calculated from the experimental distillation behavior of a mixture. A test procedure that can be carried out with laboratory columns was described for practical determination of the number of plates required for a separation as well as for checking of the calculations. Continuously operating bubble plate columns made of glass are fitted with side arms for removal of samples so that the concentration profile in the column can be established by analysis for the steady state under various conditions. The predictive power and reliability of the procedure was demonstrated for a model example.

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Theoretical Conditions for Conjugation Involving d Orbitals

By *Günter Häfelinger*[*]

HMO π-electron models are used to examine the stability of the ground state and the reactivity of cyclic π-conjugation systems with various ring sizes in which one or more p_π orbitals are replaced by atoms that contribute outer or inner d orbitals to the π system.

Taking into account the special symmetry behavior of the d orbitals, the extent of $(pd)_\pi$ overlap, and the inductive effect of the hetero atom, it is found that no unusual energy stabilization, comparable *e. g.* with that found in the systems of aromatic hydrocarbons, is to be expected, though cyclic delocalization with participation of the d orbitals is possible. Transition metal chelates with aliphatic 1,2-diimine ligands are considered as special examples.

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Procedure for Stereospecific Hydrogen-Labeling of Prochiral Centers on a Preparative Scale

By *Helmut Günther* (Lecturer), *Miguel Alizade*, *Florian Biller*, *Max Kellner*, *Hans Jürgen La Roche*, and *Helmut Simon*[*]

Stereospecifically hydrogen-labeled compounds of the type $CH\overset{*}{H}ab$ are interesting for a whole series of reasons. Hitherto only a few such compounds have been obtained on a preparative scale. Chemical synthesis by stereospecific replacement of X in a chiral compound by $\overset{*}{H}$ requires sterically pure starting material, and the quality of the products depends on the stereospecificity of the reactions $CHXab \rightarrow\rightarrow CH\overset{*}{H}ab$. Stereochemically pure forms are

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generally obtained by enzymatic reactions. According to our findings, microorganisms often catalyze hydrogen exchange in their metabolic prochiral end products. Such exchange reactions can also be effected by coupled enzyme reactions. In such work either CHHab is incubated in D_2O or H_2O/HTO, or CHHab is incubated in H_2O. In this way we obtained:

The (1*R*)- and (1*S*)-forms of [1-H]-ethanol, -propanol, and -butanol, as well as the (2*R*,3*R*)-forms of [2,3-H]-butyric, -valeric, -octanoic, -4-bromobutyric, -2-bromobutyric, and other acids.

Clostridium kluyveri ferments crotonate to acetate and butyrate. Preparative amounts of [2,3-^{2}H]-(2*R*,3*R*)butyrate can be prepared in D_2O. Similar results can be obtained with other α,β-unsaturated acids.

Synthesis and Chemistry of *N*-Chlorocarbonyl Isocyanate

By *Hermann Hagemann*[*]

ClCONCO (colorless liquid, b.p. = 64 °C) is obtained in a yield of 90% by partial hydrolysis of *N*-chlorocarbonyl isocyanide dichloride[1], the addition product of phosgene and cyanogen chloride.

This simple and very reactive iminodicarboxylic acid derivative can be used for the preparation of many compounds of this series. Both the acyl chloride group and the isocyanate group can undergo selective reactions. One outcome is a simple method for the preparation of isocyanates from alcohols, phenols, thiols, and thiophenols[2].

The combination of the two functional groups and their peculiar symmetry, which becomes clear *e.g.* in the HCl adduct, also enable *N*-chlorocarbonyl isocyanate to enter into cyclizations under particularly mild conditions.

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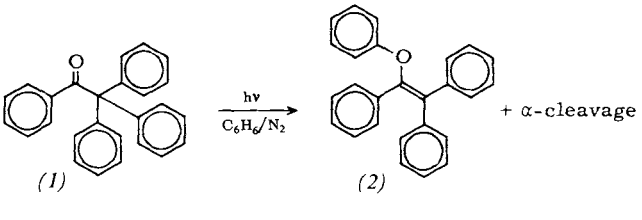
[1] *H. Hagemann* and *D. Arlt*, Dt. Pat. Anm. P 1768179-7 (April 10, 1968) Farbenfabriken Bayer.

[2] *H. Hagemann*, Dt. Pat. Anm. P 1793088 (July 31, 1968) Farbenfabriken Bayer.

Sigmatropic 1,3-Phenyl Shift in Photoexcited Phenyl Trityl Ketones

By *H.-G. Heine*[*]

On irradiation (Philips HPK 125 W, $\lambda > 300$ nm) in solution, phenyl trityl ketone *(1)* undergoes a novel photoisomerization, in which the enol phenyl ether *(2)* is formed by a phenyl shift. α-Cleavage occurs to a small extent. In the presence of triplet quenchers (*e.g.* piperylene), only the isomerization *(1)*→*(2)* is observed.



(1) *(2)*

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It is shown by the use of substituted derivatives of *(1)* that the photoisomerization proceeds with retention of the arrangement of the substituents in the migrating phenyl residue as a 1,3-(C_{sp^3}→0) shift, and not as a double 1,2-phenyl shift, which is also conceivable. The photoisomerization is formulated as a synchronous process, in agreement with the selection rules for sigmatropic reactions.

Ion-Pair Formation—Sources of Error in the Determination of Equilibrium Constants in Aqueous Solution

By *Ludwig Heck*[*]

Spectrophotometric investigations and solubility determinations on hexamminecobalt(III) salts have shown that the perchlorate ion, like all monovalent anions, forms ion pairs even in dilute aqueous solution:

$$[Co(NH_3)_6]^{3+} + ClO_4^- \rightleftharpoons [Co(NH_3)_6]^{3+}\ x\ ClO_4^-$$

By fast precipitation of hexammineplatinum(IV) chloride, carbonate, or sulfate from 0.02 M hexammineplatinum(IV) perchlorate solutions, up to 40 mole % of perchlorate ion pairs are coprecipitated.

Addition of perchlorate in the determination of the equilibrium in the system hexamminecobalt(III) ion—chloride considerably influences the constant, even if the ionic strength is kept strictly constant. This provides a simple explanation for conflicting literature data.

If a cationic species has acid properties, as *e.g.* the hexammineplatinum(IV)-complex which is easily deprotonated to its conjugate base, amidopentammineplatinum(IV)-ion, the perchlorate ion tends to associate primarily with the higher charged acid ion. Lowering the equilibrium concentration of the hexammine complex by ion-pair formation results in a decrease of its acid strength.

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A Contribution to the Investigation of Fossil Amino Acids and Peptides from Black Shales

By *Wolfgang Heller*[*]

The investigations were carried out on samples of the Upper Devonian black shales of Meschede, the Triassic bituminous shales of Monte San Giorgio (Ticino, Switzerland), and the Posidonomya shales (Lias epsilon) of Schwaben. The material was ground to a fineness suitable for analysis, and was then extracted under mild conditions. The resulting extracts were examined for free amino acids and peptides.

In the examination of a large number of samples both from Monte San Giorgio and from the Posidonomya shales of Schwaben for protein degradation products, it was found that the content of amino acids often varies very considerably in one and the same zone, even when the sampling points are only 50 cm apart. A considerable accumulation of amino acids always occurs in particular in the vicinity of

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ammonite shells with retention of the living chambers or of saurian skeletons, especially those with skin retention. It can therefore be seen that these amino acids are degradation products of animal protein.

In the vicinity of ammonite shells with retention of the living chambers and of saurian skeletons, the amino acids are separated according to their R_f values. The clay minerals have acted here as a natural partition chromatography system during the breakdown of the proteins. The migration of the amino acids is also closely related to the content of organic matter in the sediment.

So far we have detected 14 free amino acids, three tripeptides having been found in the bituminous shales of Monte San Giorgio and in the Posidonomya shales. The results obtained so far indicate that the black shales of Meschede contain only free amino acids.

Electrochemistry of Corrosion and of Corrosion Prevention

By *Ewald Heitz*[*]

The corrosion of metals in liquid media is an electrochemical process in which the corroding metal is the anode and an oxidizing agent is reduced at cathodic sites. The individual steps of the reaction can be established by the methods of electrochemical kinetics and thermodynamics. As in any heterogeneous chemical reaction, the steps consist of transport processes and reactions at phase boundaries. The reactions at phase boundaries may be electrochemical transfer reactions. However, adsorption and chemisorption processes also can be rate determining as well as preceeding and subsequent homogeneous and heterogeneous reactions. For example, the reaction course is largely known for the systems iron/nonoxidizing acids, alloyed steel/sea water, and copper/oxidizing acids.

The electrochemical mechanism of corrosion provides the basis of a series of test methods which are based in principle on the evaluation of the current-voltage curve for the metal and the solution in question. Such methods give either the instantaneous corrosion rate or the potential susceptibility of passive metals to certain types of corrosion.

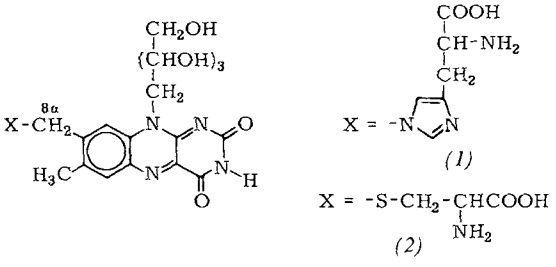
The electrolytic mechanism also provides the basis of a series of corrosion prevention methods. These include the methods of cathodic protection by the use of impressed current, active anodes, and cathodically active coatings. Mention should also be made of inhibitors, which reduce the reaction rate at both anodic and cathodic sites on the surface.

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New Flavocoenzymes

By *Sandro Ghisla, Peter Hemmerich* (Lecturer), *E. B. Kearney, T. P. Singer*, and *W. H. Walker*[*]

It is known from earlier investigations that the flavocoenzymes of succinate dehydrogenase ("SD flavin")[1] and of monoamine oxidase ("MAO flavin")[2] are flavin-adenine dinucleotide derivatives attached to the protein by covalent bonds. These flavocoenzymes have been characterized by absorption, fluorescence, and ESR spectra that differ from those of the "normal" unsubstituted flavocoenzymes. It is found in this way that the protein is bonded to the heteroaromatic flavin ring in position 8α[3]. This has been demonstrated by synthesis of 8α-substituted lumiflavin models[4], which exhibit the same spectral behavior. In work carried out in collaboration with Dr. *T. P. Singer*'s research team, the structure of these flavocoenzymes was established and it was shown that the natural products and the synthetic compounds are identical. In the case of "SD flavin" *(1)*, the linkage is formed between position 8α and the imidazole ring of a histidine, while in "MAO flavin" *(2)*, a covalent bond is similarly formed with the sulfur of a cysteine.



(1)

(2)

The course of the synthesis *via* 8α-bromoflavins and the influence of the 8α substituent on the ESR, fluorescence, and absorption spectra were discussed. Other new flavocoenzymes whose structures are still unknown are being studied at present by teams working with Dr. *Decker* (Universität Freiburg) and Dr. *Massey* (University of Michigan).

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[1] *T. P. Singer, J. Hauber*, and *E. B. Kearney*, Biochem. Biophys. Res. Commun. *9*, 146 (1962); *E. B. Kearney*, J. Biol. Chem. *253*, 865 (1960).

[2] *E. B. Kearney, J. I. Salach, W. H. Walker, R. Seng*, and *T. P. Singer*, Biochem. Biophys. Res. Commun. *42*, 490 (1971).

[3] *P. Hemmerich, A. Ehrenberg, W. H. Walker, L. E. G. Eriksson, J. Salach, P. Bader*, and *T. P. Singer*, FEBS-Lett. *3*, 37 (1969).

[4] *T. P. Singer, J. Salach, P. Bader, A. Ehrenberg, W. H. Walker, P. Hemmerich, S. Ghisla*, and *U. Hartmann*, Europ. J. Biochem., in press.

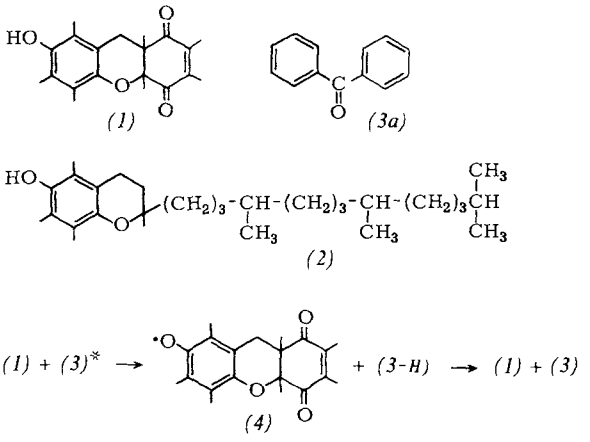
Reversible Photodehydrogenation of Diduroquinone to the Aroxyl Radical with Optically Excited Carbonyl Compounds such as Quinones, Ketones, and Xanthene Dyes

By *G. O. Schenck* and *H. Hermann* (Lecturer)[*]

The photodimer of duroquinone, the phenolic chroman *(1)*, serves as a model for the structurally related α-tocopherol [vitamin E *(2)*]. Both have characteristic inhibitor effects. On photodehydrogenation with the carbonyl compounds *(3)* duroquinone, 2,3-dimethylnaphthoquinone, 2-phenylnaphthoquinone, chloranil, benzophenone, rose bengale, and eosin, *(1)* forms the short lived aroxyl radical *(4)* and the monohydrocarbonyl compound *(3-H)*. Both radicals are reconverted by different routes into the starting materials to complete the chemical quenching cycles. The reverse reactions of *(4)* depend on the photodehydrogenating *(3)* used. The different kinetics of the back reactions of the various systems are explained by the involvement of

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H-bonded radicals and H-bonded radical pair complexes. In the photochemical reaction of *(1)* with benzophenone *(3a)* the radicals are synchronously regenerated in part

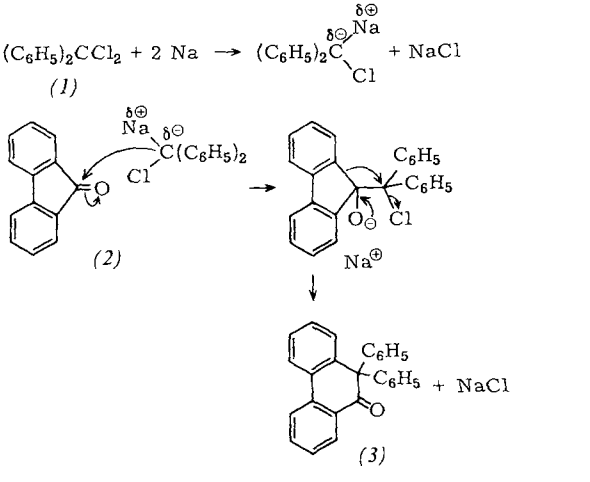


from the primary H-bonded radical pair complex, the dissociation of which is followed by further reverse reactions.—The results of flash-photolytic studies on duroquinone, 2,3-dimethylnaphthoquinone, 2-phenylnaphthoquinone and chloranil in benzene, ethanol and cyclohexane are described.

Rearrangement Induced by Nucleophilic Addition of an α-Haloorganometallic Compound

By *B. J. Herold* (Lecturer) and *J. J. R. P. Queiroga*[*]

When a solution of equimolar quantities of dichlorodiphenylmethane *(1)* and fluorenone *(2)* in diethyl ether is allowed to react with two equivalents of sodium, 10,10-diphenyl-9-phenanthrone *(3)* is formed[1]. To elucidate



the reaction, it is necessary to establish whether the metal reacts first with fluorenone (in which case the dianion would be formed) or whether it reacts first with *(1)* to form the α-haloorganometallic compound. It has been possible to rule out the first of these two possibilities. A reaction course has been proposed in which α-chlorobenzhydrylsodium adds as a nucleophile to fluorenone, and the addition product undergoes a rearrangement that may be regarded as an otherwise unknown base-catalyzed analog of the Tiffeneau rearrangement.

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[1] *W. Schlenk* and *E. Bergmann*, Liebigs Ann. Chem. *463*, 209 (1928).

Spallogenic ^{53}Mn ($T \approx 2 \times 10^6$ a) and the Measurement of a Depth Effect in a Material Exposed to Cosmic Radiation

By *Wilfrid Herr* (Lecturer), *Ulrich Herpers*, and *Robert Wölfle*[*]

Accurate determinations of long-lived spallation nuclides, *e.g.* of ^{53}Mn ($T \approx 2 \times 10^6$ a), are currently of interest for the determination of "radiation ages" and the detection of possible variations of the cosmic flux. An extremely economical analytical method has been developed for the investigation of meteorites and lunar samples. Spallogenic ^{53}Mn, a K emitter, is difficult to count directly; however, the nucleus has a high neutron cross section. By long term exposure in a nuclear reactor for 42 days ($\Phi_{therm} = 8 \times 10^{12}$ n/cm^2·s), it is possible to convert the nuclide into ^{54}Mn, which can be easily detected because of its characteristic 0.84 MeV γ radiation. The influence of the interfering $^{54}Fe(n,p)^{54}Mn$ and $^{55}Mn(n,2n)^{54}Mn$ reactions has been investigated in detail. A practically "carrier-free" ^{52}Mn carrier prepared by the reaction $^{52}Cr(p,n)^{52}Mn$ was used to allow control of the chemical yield of manganese. In a rock from the Sea of Tranquillity a ^{53}Mn depth profile was found which can be attributed to the interaction and overlapping of "solar wind" and primary cosmic radiation.

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Isotopic Effects of Calcium in Heterogeneous Exchange Equilibria

By *K. G. Heumann* (Lecturer) and *K. H. Lieser*[*]

Several heterogeneous exchange reactions have been examined for isotope fractionations.

The isotopic ratio of calcium was determined by means of a mass spectrometer with a thermal ion source.

In the systems $CaCO_{3(solid)} / Ca^{2+}_{(dissolved)}$ and GBHA-$Ca_{(solid)} / Ca^{2+}_{(dissolved)}$ (GBHA = glyoxal bis(2-hydroxyanil)), it was possible to show by multi-stage experiments that the elementary effect is less than 0.5 ‰ per mass unit. It follows that no isotope fractionation is to be expected in precipitations or crystallizations of calcium salts.

In the case of the exchange equilibrium between calcium on a cation exchanger and Ca^{2+} ions in solution, the elementary effect could be determined directly only when Dowex A1 was used. This led to 20.5 ‰ enrichment of ^{48}Ca in the solution. Enrichment of ^{48}Ca in the solution was also found with Dowex 50 by multiplication of the elementary effect. The isotopic effect was found to depend on the concentration of the hydrochloric acid used as the eluent.

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The Elastic State of High Polymers

By *Martin Hoffmann*[*]

In a lecture surveying the highly elastic deformation of polymers, experimental findings were compared with the predictions of the existing theory of rubbery elasticity. The differences are large, but can be quantitatively traced to entanglement.

Twenty vulcanizates of a random butadiene-acrylonitrile-(18) copolymer with different degrees of crosslinking were swollen in several solvents. They were then stretched at different speeds or examined at various elongations for stress relaxation before removal of the load and for specimen length relaxation after removal of the load. The elastic elongation can be calculated from the length of the stretched specimen only 0.1 s after the start of loading (or on elongation at $d\lambda/dt = 1\ [s^{-1}]$) and the initial length. However, the same elongation law is obtained if the length of the specimen after prolonged loading is divided by the length found 0.1 s after the removal of the load: The entangled filament molecules form a network with exchangeable bonds.

This gives an elongation law that is completely free from arbitrariness. It can be approximately evaluated according to *Mooney* for the partial moduli $2C_1$ and $2C_2$. The former describes the effect of principal-valence crosslinks, and the latter the effect of entanglements. On swelling, $2C_2$ decreases with the square of the polymer concentration, and $2C_1$ only with the cube root. The sum of $2C_1$ and $2C_2$ is independent of $2C_1$ for unswollen, moderately strongly crosslinked specimens, since the entanglements are replaced by crosslinks. The elongation law for entangled chains is different from that for crosslinked chains. The number of effective entanglements depends not only on the time under load, but also (on geometric grounds) on the elongation. The causes are discussed and yield a quantitative formulation of the actual elongation process.

Finally, it is pointed out that to be of industrial interest, an elastomer must be easy to process and to vulcanize, as well as having good properties in the vulcanized state.

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Reaction of Recoil Products with Free Radicals

By *Peter Hoffmann, Knut Bächmann* (Lecturer), *Helmut Klenk, Werner Bögl*, and *K. H. Lieser*[*]

We investigated the reaction of recoil products of Ra-224 with alkyl radicals formed by thermal decomposition of tetraalkyllead. The Ra-224 was deposited on a gold foil by evaporation of a 0.2 N HCl solution or by vapor deposition. The products of the free-radical reaction were transported through a distillation system to the measuring point and identified by γ spectrometry. The chemical yields were 65—90% for Pb-212, 95—100% for Bi-212, and 45—85% for Tl-208, based on the recoil yields, which were determined separately. It was possible to compare these experiments with inert gas experiments, in which hydrogen, nitrogen, helium, argon, acetone, diethyl ketone, and undecomposed tetraalkyllead compounds were led over the source and used for the transport of Rn-220.

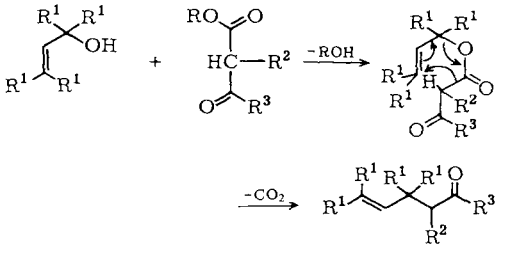
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Reaction of Allyl Alcohols with Acetoacetic Acid Derivatives (Carroll Reactions)

By *Werner Hoffmann*[*]

Carroll found that allyl alcohols react with acetoacetic esters at 160 to 200 °C with elimination of alcohol and carbon dioxide to form γ,δ-unsaturated ketones[1]. These reactions have become very important in terpene chemistry. They are used *e.g.* for the preparation of intermediates for industrial vitamin A and vitamin E syntheses.

The relation between constitution and reactivity of the starting materials is shown for this type of reaction by variation of the substituents in the alcohol and ester components and kinetic investigation of the reactions.



R = alkyl
R^1 = H or alkyl
R^2 = H, Cl, alkyl, COO-alkyl, or —CH=CH—CO-alkyl
R^3 = H, alkyl, or O-alkyl

The reactivity of the acetoacetic ester derivatives can be increased by introduction of electron-attracting substituents or by increased enolization of the hydrogen on the methine group. In the allyl alcohols, the reactivity decreases from the tertiary *via* the secondary to the β-substituted primary compounds. Some syntheses of terpenoid substances from the products of these reactions are illustrated.

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[1] *M. F. Carroll*, J. Chem. Soc. *1940*, 704.

The Decomposition of Organolead Halides $R_{4-n}PbX_n$ and Attempts to Prepare Organolead Halides that Occur as Intermediates

By *Friedo Huber* (Lecturer), *J. Gmehling, H.-J. Haupt*, and *H. Lindemann*[*]

$Alkyl_2PbX_2$ decomposes in aqueous solution in the presence or in the absence of foreign salts MX in accordance with the overall equation (1), which is the result of a primary disproportionation (2) and a subsequent decomposition (3) (alkyl = CH_3).

$$2\,(CH_3)_2PbX_2 \rightarrow (CH_3)_3PbX + PbX_2 + CH_3X \quad (1)$$
$$2\,(CH_3)_2PbX_2 \rightarrow CH_3PbX_3 + (CH_3)_3PbX \quad (2)$$
$$CH_3PbX_3 \rightarrow PbX_2 + CH_3X \quad (3)$$

(1) is first order, irrespective of the concentration of MX. The reaction rate increases considerably with increasing

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polarizability of the anion. (2) is the rate-determining step, and proceeds as a ligand-exchange reaction. Higher temperatures are required for the decomposition of $Alkyl_3PbX$. Attempts to prepare the unstable intermediates $RPbX_3$ ($X \neq$ carboxylate) led to the first preparation of complexes of phenyllead trihalides, *e.g.* $[pyH]_2[C_6H_5PbCl_5]$, $[(C_6H_5)_4As][C_6H_5PbCl_4]$, $[(C_6H_5)_4P][C_6H_5PbBr_4]$ and of $C_6H_5PbCl_3$ as ether adduct and as the py-adduct $C_6H_5PbCl_3 \cdot 2py$.

Synthetic Resins in Elastomer Adhesives

By *Kurt Hultzsch*[*]

Synthetic resins can fulfil important functions in elastomer adhesives. The physical and chemical interactions between resins and elastomers and their causes are discussed and presented as a synopsis. The resins act as a sort of solid solvent, and increase the tackiness of the elastomers. They may also increase the cohesion and hence the heat resistance of adhesives by a kind of reinforcing effect. In the case of polychloroprene, there is also a possibility of an irreversible increase in cohesion as a result of self-crosslinking of the elastomer with ZnO and MgO. It was shown by vulcametric experiments that added resin, as a diluent, inhibits this process on the one hand. On the other, "base-reactive" resins favor vulcanization after their reaction with the metal oxides, presumably because the basic reactants are now present in a homogeneously dissolved form. No resin vulcanization has been detected. The aging behavior of the adhesives may also be affected by resins.

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Recent Developments in Chromatography: Column Liquid- and Supercritical Fluid Chromatography

By *J. K. F. Huber*[*]

In the past few years new forms of chromatography have been developed in which gases under high pressure or supercritical fluids have been employed as the mobile phase. A continuous transition between gas- and liquid-chromatography has thus been accomplished. The non-ideality of the carrier gas increases with increasing pressure; the partition coefficient becomes a function of the pressure and type of carrier gas. At the same time, the diffusion coefficient decreases. Beyond the critical point, large changes in the partition coefficient occur and its temperature dependence is reversed.

Results of a series of investigations have shown that the partition coefficient can be reduced by about two orders of magnitude by working with supercritical phases. Hence, low volatile compounds such as polycyclic aromatic hydrocarbons or dialkylphthalates can be analyzed by this technique.

The oldest chromatographic method, column liquid chromatography, is at present experiencing a second renaissance. This is due, on the one hand, to a more complete knowledge of the theory of the chromatographic process and, on the other hand, to the fact that the limitations of other chromatographic methods are becoming more clearly defined. Advances made on the theoretical side have made it possible to describe all forms of elution chromatography. The verification of theory for the case of column liquid chromatography demonstrates the influence of the various process variables. From the practical point of view it can be concluded that columns should be used which are packed with very fine-grain material and through which eluent flows relatively rapidly; thus, a high inlet pressure is required. Data for the optimization of separation referred to speed or dilution of sample can be derived theoretically and confirmed by experiment.

Most useful are methods by which the partition coefficients can be predicted. Promising results have been obtained for steroids in ternary liquid-liquid systems.

The performance of modernized column liquid chromatography is illustrated *e.g.* by the rapid separation of steroids, biocides, and non-ionic surfactants as well as by the residue analysis and trace determination of steroids in urine and blood plasma.

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Chromium Dioxide Pigments. Dependence of Some Properties (Particularly Magnetic) on the Particle Size

By *Franz Hund*[*]

The economic development of magnetic recording with γ-Fe_2O_3 pigments is first discussed. γ-Fe_2O_3 and CrO_2 pigments are then compared with regard to suitability for use as magnetic recording substrates. The CrO_2 pigments can be prepared by thermal decomposition of pure chromyl chloride, pure chromium trioxide, or chromium trioxide in the presence of foreign or intrinsic modifiers that control the particle size. The coercive force and the signal-to-noise ratio depend on the particle size of the chromium dioxide pigments prepared by the hydrothermal two-step process[1]. When chromium dioxide is used as the catalyst in the air oxidation of SO_2 and HCl, the yield increases with decreasing particle size.

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[1] *F. Hund* and *W. Abeck*, US-Pat. 3371043 (1963/1968), Farbenfabriken Bayer AG.

Rapid and Simple Enrichment of Trace Elements in High-Purity Zinc by Partial Dissolution of the Matrix in the Presence of Mercury

By *Ewald Jackwerth* (Lecturer) and *Eva Döring*[*]

During the dissolution of zinc in hydrochloric acid, a definite accumulation of traces of metallic impurities is observed on the surface of the residue. Though the phenomenon is of little value in this form, its effectiveness and reproducibility are decisively improved if the zinc is coated with a thin layer of mercury before dissolution. The trace elements Bi, Cu, Cd, Pb, Co, Ni, Sn, Tl, In, Ag, Au, and Pd that are present as impurities then remain almost quantitatively in the residue. The addition of 1—2% of mercury

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based on the zinc is sufficient for the amalgamation, and has practically no effect on the rate of dissolution.

For analysis of the concentrated trace metals, mercury spheres that still contain about 50—100 mg of Zn are dissolved in nitric acid. The concentrated elements are determined photometrically and polarographically after separation of the mercury. The correctness of the analyses has been checked on spectrochemically analyzed material.

The Loose Connection between Electron Configuration and Chemical Behavior of the Transuranics

By *Christian Klixbüll Jørgensen*[*]

According to the "Aufbau Principle" of the Periodic System, the electrons successively fill n l-shells, each fully-occupied shell containing at most $(4l+2)$ electrons. Seen from a quantum-mechanical point of view[1] the angular functions are homogeneous polynomials of degree l in the Cartesian coordinates, and high l values (such as 3 for f electrons) go along with unusually large amounts of angular kinetic energy, much larger than the ionization energy in rare earths. The competition between different shells often depends on the ionic charge. Thus, there are fourteen lanthanides between lanthanum ($Z=57$) and lutetium ($Z=71$) yet eleven of them have only two valence electrons (6s) in the neutral atom. *Klemm* showed from the physical properties of the metals that they have as many 4 f electrons as their trivalent ions; only europium and ytterbium are bivalent.

Goldschmidt suggested that thorium ($Z=90$) started a new, mainly quadrivalent 5 f series, and *Ephraim* has pointed out that uranium(IV) compounds have narrow absorption bands due to transitions between the energy levels of two 5 f electrons. When neptunium and plutonium were first produced it was thought for a while that they were the first members of a predominantly hexavalent 5 f series. On the basis of the properties of the succeeding elements, Seaborg developed the "actinide hypothesis" which states that the 5 f shell is filled in all chemical systems containing more than 86 electrons. With exception of the metallic elements and alloys, this hypothesis has been confirmed by spectroscopic studies.

However, there is not necessarily a connection between exclusive trivalency and presence of f electrons. In fact, only about six transplutonium elements are predominantly trivalent; the word "actinide" is rather an unfortunate choice. Mendelevium ($Z=101$) and nobelium ($Z=102$) are usually bivalent. A closer theoretical analysis[2,3] shows that this variation is connected with a parameter $(E-A)$ and the hydration or Madelung energy which represents the chemical influences. Elements containing shells with small average radii such as 3 d, 4 f, and 5 g have a low and rather constant oxidation state, whereas the elements with other shells such as 4d, 5d, and 5f have higher and more variable oxidation states at the beginning of electron-filling (cf. Nb, Mo, Tc, Ru with V, Cr, Mn, Fe) but lower oxidation states as the shells become fully occupied (cf. Ag with Cu).

A few atoms with $Z=103$, 104, and 105 have been made in California and in Russia, and perhaps a few with $Z=112$ at CERN in Geneva; these elements, like element 114, should be normal post-transition elements, whereas the elements between, which probably can be prepared according to the nucleonic shell model of *Maria Goeppert-Mayer* and *Hans Jensen* belong to transition groups. The element with $Z=126$, with its four 5 g electrons, is exclusively tetravalent. Dwi-lead ($Z=164$) is palladium-like and has eight 7 d electrons (and two 8 s and two 8 p electrons, which are highly stabilized for relativistic reasons). The element with $Z=184$ should be a super-rhenium with oxidation states between 4 and 12 and eight to zero 6 g electrons with large average radii[3].

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[1] *C. K. Jørgensen:* Orbitals in Atoms and Molecules. Academic Press, London 1962.

[2] *C. K. Jørgensen:* Oxidation Numbers and Oxidation States. Springer-Verlag, Berlin 1969.

[3] *C. K. Jørgensen:* Modern Aspects of Ligand Field Theory. North-Holland Publ. Co., Amsterdam 1971.

New Methods for the Solid-Phase Synthesis and for the Analysis of Polypeptides

By *Günther Jung* (Lecturer), *Eberhard Breitmaier*, *Wolfgang Voelter*, and *Ernst Bayer*[*]

Difficulties that arise with certain combinations of protective groups can be avoided by the use of alkyl-substituted supports based on polystyrene. The number of incorrect and incomplete sequences that are frequently formed in solid-phase syntheses and the synthesis time can be reduced in some cases by a column process using a silicate support. This new type of support, which contains covalent Si—O—C and Si—C bonds, can be modified in any desired way on the surface, and can be used not only for the synthesis of biopolymers but also in preparative and analytical chromatographic procedures.

Pulse Fourier transform ^{13}C-NMR spectroscopy is particularly suitable for the determination of the redox and dissociation equilibria of cysteinyl peptides. The enantiomeric purity of amino acids can be determined independently of other methods from the ^{19}F-NMR spectra of derivatives with chiral sensors containing fluorine. This purity can also be determined by gas-chromatography on chiral dipeptide phases.

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The Aminoisoxazole-Pyrazolone and Retro-Aminoisoxazole Rearrangements

By *Hans Junek*[*]

Examination of the products obtained from benzohydroxamoyl chlorides or nitrile oxides with cyanoacetic acid derivatives shows that they are not the expected 5-amino-3-phenylisoxazole-4-carbonitriles, but the isomeric pyrazolones. This can be demonstrated by acylation experiments, degradation, and rearrangement, as well as by comparative IR and NMR spectroscopy. A mechanism based on a rearrangement of the initially formed unstable isoxazoles is proposed for the formation of the pyrazolones. This aminoisoxazole-pyrazolone rearrangement is due to

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a specific influence of the nitrile group. This effect is eliminated by hydrolysis of the nitrile group, and a retro-amino-isoxazole rearrangement can then occur.

The Decay of the Isomers of Rhenium-190

By *Norbert Kaffrell* (Lecturer) and *Norbert Trautmann*[*]

The β and γ radiation of 2.8 min ^{190g}Re and 2.8 h ^{190m}Re have been investigated with scintillation and semiconductor detectors. Two Ge(Li) diodes and a matrix of 1000 × 1000 channels were available for γ-γ coincidence measurements. Both isomers were prepared by irradiation of natural osmium with 14 MeV neutrons followed by chemical separation of the rhenium fraction. The 2.8 min isomer was also obtained by activation of enriched ^{192}Os with bremsstrahlung.

Spin and parity of $J^{\pi}=2^-$ and the configuration pn[402↑]—[505↓] have been assumed for the 2.8 min ground state. The β^- decay feeds almost exclusively the $J^{\pi}=3^-$ level of ^{190}Os at 1387 keV. This level is assigned the configuration pp[402↑]—[505↑], since according to the log ft value of the β transition it must be an allowed, unhindered transition. The 2.8 h activity decays mainly by an isomeric transition into the ground state of ^{190}Re. A smaller component feeds levels in ^{190}Os by direct β decay. The ground state rotational and γ-vibrational bands are excited up to spins of $J=8$. A decay scheme for both isomers was proposed and discussed.

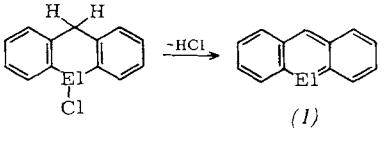
[*] Dr. N. Kaffrell and Dr. N. Trautmann
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System with π Bonds to the Elements Boron, Silicon, and Arsenic

By *Peter Jutzi*[*]

(p-p)π bonds between carbon and the elements boron, silicon, and arsenic, which are of interest from the standpoint of bond theory, are practically unknown at present. 9,10-Dihydroanthracene derivatives containing hetero atoms instead of C-9 form resonance-stabilized C-element (p-p)π bonds under specific conditions.

Novel heteroaromatic compounds *(1a)* and *(1b)* are formed by intramolecular HCl elimination from 9-chloro-9,10-dihydro-9-bora- and 9-arsa-anthracene.



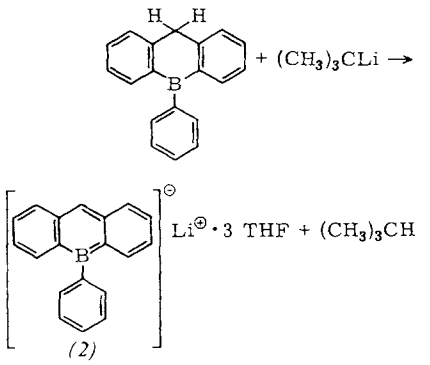
(1)

(1a), El = B←S(CH$_3$)$_2$
(1b), El = As

Metalation of 9-phenyl-9,10-dihydro-9-bora-anthracene in position 10 leads to the 9-phenyl-9-bora-anthracene anion *(2)*.

The postulated structures are confirmed by UV and NMR spectra and by chemical reactions.

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(2)

A 9-sila-anthracene is found only under mass-spectrometric conditions. Bulky ligands R and R′ in the 9-chloro-9R-10R′-9,10-dihydro-9-sila-anthracene system have a decisive effect on the elimination of HCl.

Significance of Chemical Surface Reactions in Electrode Processes

By *Bertel Kastening*[*]

Many electrode processes are coupled with chemical reactions that precede or follow the charge transfers. Processes of this type can proceed as homogeneous or as heterogeneous reactions. The conditions for the reaction in the latter case are different from those for pure homogeneous reactions.

If strong interaction with the electrode is present, charge transfer, chemical reactions, and change of solvation may take place as concerted reactions rather than as individual steps and may be looked at as potential-dependent adsorption/desorption phenomena.

In the case of weak interaction (adsorption resulting from the lyophobic character of the substrate), the following particular conditions must be considered:

1. The rate depends on the surface concentration and hence on the adsorptivity.
2. The reaction proceeds in an environment that differs from the bulk of the solution, and under the influence of a very strong electric field, both effects resulting in a change of charge distribution within the molecule and in a particular orientation sometimes effecting stereospecific reactions.
3. The reaction takes place directly at the electrode. It may, therefore, proceed unidirectionally towards an unfavored species, if the latter is immediately displaced by a secondary charge transfer.

Valuable information has been obtained by investigations in the presence of surface-active substances not involved in the process but hindering surface reactions by replacing the substrate and reducing its adsorptivity. By this means the author has shown that a heterogeneous proton transfer reaction (*i.e.* $O_2^- + H_2O \rightarrow HO_2 + OH^-$) is responsible for the reversible character of the O_2/HO_2^- couple in aqueous alkaline solutions. Because they ignored heterogeneous reactions, other authors reached incorrect conclusions concerning the mechanism and the thermodynamic and kinetic parameters in this case.

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Radiation-Induced Crosslinking in Polyisoprene

By *Hans Katzer* (Lecturer) and *Helmut Heusinger*[*]

Polyisoprene was prepared by the living-polymer method. This leads mainly to 1,2 and 3,4 addition. The radiation-induced crosslinking was investigated in the pregel and gel region. The G values for crosslinking calculated from the gel contents and the corresponding molecular weights range from 13.5 to 38, and depend on the molecular weight. Our experimental results can be described quantitatively if one assumes that the crosslinking, as in the case of the unsaturated polyesters investigated by *Charlesby*, proceeds by a chain reaction with consumption of double bonds. The decrease in the content of double bonds during irradiation was followed by IR spectroscopy. However, the G value for the decrease in the content of double bonds was found to be greater by a factor of 13 than the G value for crosslinking. We assume that a cationic chain reaction occurs on irradiation, and that this leads in an intramolecular reaction to cyclized units and in an intermolecular reaction to crosslinking.

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Formation of Hydrocarbons on Heating of Saturated Fatty Acids and their Methyl Esters

By *H.-J. Kleinau*[*]

In oxidation experiments with saturated fatty acids and their methyl esters, numerous reaction products had already been identified. However, unknown substances were also recorded on gas chromatography. More recent investigations showed that these included hydrocarbons. Hydrocarbons have also been detected when the material under investigation was heated in the absence of oxygen. Their formation can therefore be attributed to thermal decomposition of the fatty acids.

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Aldol Condensation of Trihaloacetaldehydes with Aliphatic Ketones

By *Eberhard Kiehlmann*[*]

Fluoral and chloral react with aliphatic ketones in glacial acetic acid to form 1,1,1-trihalo-2-hydroxy-4-alkanones, whereas bromal does not. With diethyl ketone and cyclohexanone, two chromatographically separable diastereoisomeric ketols, which epimerize in reactions on the preparative scale, are obtained. The rate constant for the epimerization was measured. Methyl ethyl ketone condenses both in the α-CH_2 group and in the α-CH_3 group to form three isomeric ketols, the former condensation predominating. Methyl isobutyl ketone reacts with chloral exclusively in the α-methyl group, whereas fluoral also adds to the methylene group. Higher methyl alkyl ketones also react mainly on the α-methyl group, on steric grounds.

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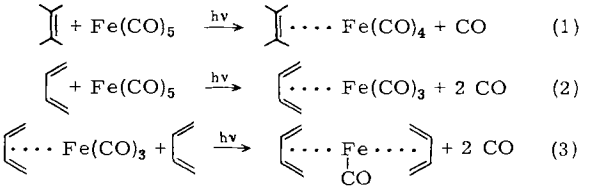
The orientation in the aldol condensation of trihaloacetaldehydes with unsymmetrical aliphatic ketones is kinetically controlled; no α,β-unsaturated ketones are formed.

Comparison of the above results with the rate constants for the exchange of hydrogen atoms in the α positions of the corresponding ketones against deuterium shows that the addition of the enol form of the ketone to the carbonyl group of the aldehyde molecule is the rate-determining step.

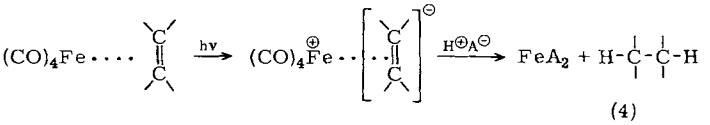
Photochemical Synthesis and Transformation of Olefin-Carbonyliron Compounds

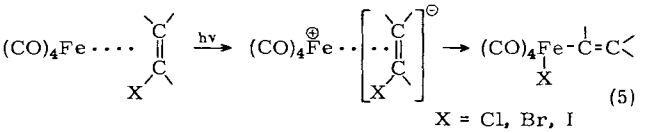
By *Ernst Koerner von Gustorf* (Lecturer), *Friedrich-Wilhelm Grevels*, *Mrinal K. Das*, *Jürgen Buchkremer*, and *Zorka Pfajfer*[*]

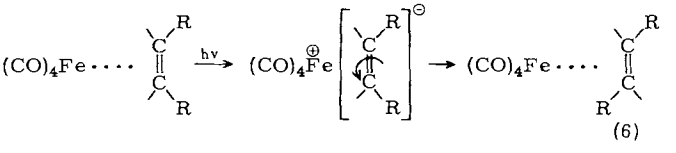
The photochemical reactions (1)—(3) represent preparatively useful routes for the preparation of monoolefin-, diene-, and bis(diene)-carbonyliron compounds.



The individual steps of the successive substitution of CO can be attributed to the intramolecular or intermolecular attack of a π system on charge-transfer ($d_{Fe}\rightarrow\pi^*_{C=C}$) excited molecules. The direction of the charge transfer is shown by reactions (4)—(6).







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Phosphorylides as Polymerization Initiators

By *Heinz Klippert* (Lecturer) and *Helmut Ringsdorf*[*]

Phosphorylides $R_3P{=}CH{-}X$ and $R_3P{=}CH_2\cdot LiBr$ (R = alkyl and aryl, X = H, $Si(CH_3)_3$, and CO—R), as basic compounds, can initiate the anionic polymerization of vinyl monomers. In the cases of methacrylonitrile and

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methyl methacrylate, the ylides are incorporated into the polymers as end groups, as has been shown by analysis and by IR and mass spectroscopy.

$$R_3P{=}CH_2 + CH_2{=}CHR' \rightarrow R_3\overset{\oplus}{P}{-}CH_2{-}CH_2{-}\overset{\ominus}{C}HR'$$

For the salt-free ylides, the ability to act as initiators depends on the basicity of the ylide carbanion; however, the structure of these ylides has no measurable effect on the molecular weight of the resulting polymers or on the stereocontrol of the reaction. On initiation with ylides containing salts, on the other hand, the tacticity and the polymer growth rate depend on the substituents on the hetero atom of the ylide.

Determination of Charge Distribution in Mass Chains in the Region of the Closed 50-Neutron Shell in the Thermal-Neutron Induced Fission of ^{235}U

By *J.-V. Kratz* (Lecturer) and *Günter Herrmann*[*]

By fast chemical separation of arsenic and selenium as volatile hydrides from the mixture of fission products, arsenic nuclides with half-lives down to 0.3 s and selenium nuclides with half-lives down to 1.4 s were identified and their mass assignment verified by milking of daughter and grand-daughter activities. ^{87}Se, ^{88}Se, ^{84}As, ^{85}As, and ^{86}As were detected as delayed-neutron precursors. Isomeric states were observed in ^{82}As and ^{84}As. Fractional cumulative yields of arsenic and selenium isotopes were measured in the mass chains 83, 84, 87, and 88, taking into account the half-lives and branching ratios found, and were used to determine the most probable nuclear charge and the width of the Gaussian dispersion curves. The results show that in the thermal-neutron induced fission of ^{235}U, fission products with mass numbers 84 ± 1 are formed preferentially with a charge density that deviates from that of neighboring mass chains. This observation could correspond to a shell effect on the charge distribution of primary fission fragments. However, calculations show that the effect can also be explained by a shell-dependent evaporation of prompt neutrons.

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The Base-Catalyzed Reaction of Organic Hydroperoxides with Electron-Poor Olefins

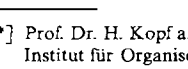
By *Heinz Kropf* (Lecturer) and *Michael Ball*[*]

Organic hydroperoxides react with electron-poor olefins in the presence of basic catalysts either to form the dialkyl peroxides[1,2] or to form epoxides[3-5] in a reaction analogous with the epoxidation of α,β-unsaturated ketones with H_2O_2 as found by *Weitz* and *Scheffer*[3].

$$RO_2H + OH^{\ominus} \rightleftharpoons RO_2^{\ominus} + H_2O \quad (1)$$

$$RO_2^{\ominus} + CH_2{=}CH{-}X \rightleftharpoons RO_2{-}CH_2{-}\overset{\ominus}{C}H{-}X \quad (2)$$

$$RO_2{-}CH_2{-}\overset{\ominus}{C}H{-}X + H_2O \rightleftharpoons RO_2{-}CH_2{-}CH_2{-}XOH^{\ominus} \quad (3)$$



$$+ RO^{\ominus} \quad (4)$$

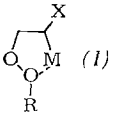
[*] Prof. Dr. H. Kopf and Dipl.-Chem. M. Ball
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On the basis of our results[2], particularly with esters of vinylsulfonic acid and divinyl sulfone, it does not seem possible to distinguish these two reaction directions on the basis of the thermodynamic acidity series

$$-NO_2 > -SO_3R > -SO_2R > -CHO > -COR > -COOR > -CN > \approx$$
$$\approx CONH_2 > -CO_2^{\ominus}$$

(the epoxides should be obtained with strongly acidifying substituents[4]).

On the other hand, a relationship is found with the lifetime of the intermediate carbanion, *i.e.* the rate of protonation as the ratio of the kinetic and thermodynamic acidities of the peroxides obtained, as is also shown by the dependence of the yields of dialkyl peroxide on the concentration of alkali and solvent. The influence of the nature of the alkali (peroxide yields increasing in the order KOH < NaOH < LiOH) suggests that the elimination to form the epoxide proceeds *via* a cyclic transition complex *(1)*. This view is also supported by the fact that the reactions with H_2O_2 lead almost exclusively to the epoxides.



(1)

[1] *D. Harman*, US-Pat. 2508256 (1948) and Brit. Pat. 658816 (1948), Shell Development Co.

[2] *H. Kropf et al.*, Tetrahedron *26*, 1347 (1970); Liebigs Ann. Chem. *743*, 151 (1971).

[3] *E. Weitz* and *A. Scheffer*, Ber. dtsch. chem. Ges. *54*, 2327 (1921).

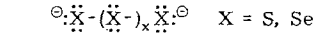
[4] *N. C. Yang* and *R. A. Finnegan*, J. Amer. Chem. Soc. *80*, 5845 (1958).

[5] *G. B. Payne*, J. Org. Chem. *25*, 275 (1960).

Phosphorus Analogs of the Polychalcogenide Chelates

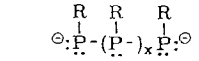
By *Hartmut Köpf*[*]

Like the polychalcogenide dianions



X = S, Se

which form a series of stable tetrachalcogenide 5-membered and pentachalcogenide 6-membered chelates $(C_5H_5)_2MX_4$ (M = Mo, W) and $(C_5H_5)_2MX_5$ (M = Ti, V) with metallicenium dications[1-4], the electronically analogous chain "dianions" of terminally *P,P'*-dimetallated organopolyphosphanes



which are obtainable by reductive cleavage of organocyclophosphanes, can combine as bidentate donor ligands with transition metal ions to form chelate-like coordination compounds. Thus in reactions of metallocene dihalides with 1,4-dipotassium 1,2,3,4-tetraphenyltetraphosphane and 1,5-dipotassium 1,2,3,4,5-pentaphenylpentaphosphane *e.g.* in accordance with

$$(C_5H_5)_2MCl_2 + K_2P_5(C_6H_5)_5 \rightarrow (C_5H_5)_2MP_5(C_6H_5)_5 + 2\,KCl$$

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the monomeric, extremely readily oxidized complexes $(C_5H_5)_2Ti(PC_6H_5)_5$ (deep violet), $(C_5H_5)_2Zr(PC_6H_5)_5$ (orange-red), and $(C_5H_5)_2Mo(PC_6H_5)_4$ (red), for which cyclic structures with a metal-substituted phosphorus ring as a chelate system are conceivable, can be isolated.

[1] *H. Köpf, B. Block*, and *M. Schmidt*, Chem. Ber. *101*, 272 (1968).

[2] *H. Köpf*, Angew. Chem. *81*, 332 (1969); Angew. Chem. internat. Edit. *8*, 375 (1969).

[3] *H. Köpf, W. Kahl*, and *A. Wirl*, Angew. Chem. *82*, 814 (1970); Angew. Chem. internat. Edit. *9*, 801 (1970).

[4] *H. Köpf, A. Wirl*, and *W. Kahl*, Angew. Chem. *83*, 146 (1971); Angew. Chem. internat. Edit. *10*, 137 (1971).

Molecular and Crystal Structures of Some Ni(0) Complexes

By *Carl Krüger* (Lecturer), *B. L. Barnett*, and *Y.-H. Tsay*[*]

Elementary nitrogen is fixed by bis(tricyclohexylphosphane)nickel as bis[bis(tricyclohexylphosphane)nickel]dinitrogen *(1)*[1], $[(C_6H_{11})_3P]_2NiN_2Ni[P(C_6H_{11})_3]_2$. X-ray structure analysis of *(1)* shows a linear Ni—N—N—Ni system (Ni—N: 1.78 Å, N—N: 1.12 Å). The P_2Ni groupings are twisted through 105° with respect to each other, with the result that an inclusion effect is produced with regard to the nitrogen by four of the cyclohexyl groups. A similar twisting has also been observed in the case of bis[1,3-bis(dicyclohexylphosphino)propanenickel hydride] $\{[(C_6H_{11})_2P(CH_2)_3P(C_6H_{11})_2]NiH\}_2$.

Comparative studies on several compounds containing σ-Ni—C bonds are also described. The X-ray structural analysis of tricyclohexylidenephosphoranetricarbonylnickel $(C_6H_{11})_3PCH(CH_3)Ni(CO)_3$ shows a comparatively elongated bond (2.097 Å) between the tetrahedrally hybridized carbon of the ethylidene group and nickel. The corresponding Ni—C distance in the square-planar compound tricyclohexylphosphanemethylnickel pentanedionate $(C_6H_{11})_3PNiCH_3C_5H_7O_2$ is 1.94 Å.

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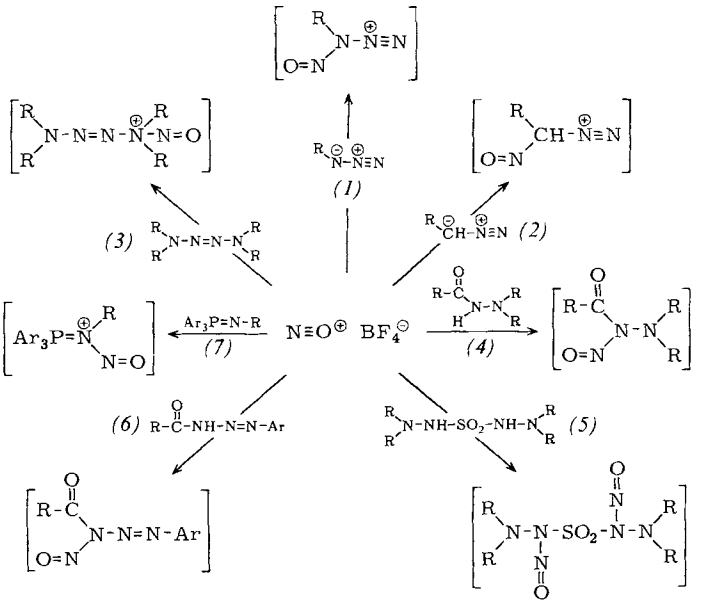
[1] *P. W. Jolly, K. Jonas, C. Krüger*, and *Y.-H. Tsay*, J. Organometal. Chem., in press.

Electrophilic Nitrosation with Nitrosyl Tetrafluoroborate

By *Richard Kreher* (Lecturer), *Hans Hennige*, and *Manfred Schmidt*[*]

The complexing of azides with Lewis acids has been systematically studied by us as a method for the production of *N*-diazonium ions[1]. A logical extension of this work is the nitrosation of organic azides *(1)* with nitrosyl tetrafluoroborate[2]. An independent route to *N*-diazonium salts, which are of interest as precursors of nitrenium ions[3], should also be provided by the reactions of 2-tetrazenes *(3)*, of acylated hydrazines *(4)*, and of *N,N'*-sulfonyldihydrazines *(5)* with the same electrophile.

According to our findings, 1-acyl-3-aryltriazenes *(6)* and substituted iminophosphoranes *(7)* with a nucleophilic nitrogen atom can be nitrosated with the reactive nitrosyl tetrafluoroborate under mild conditions[4]. These reactions provide an elegant route to reactive nitroso compounds, which cannot generally be isolated, and which enter into fragmentation reactions that are of interest from the mechanistic standpoint. The universal importance of these secondary reactions in connection with the production of reactive cationic intermediates was discussed.



[1] N_2 eliminations under the influence of Lewis acids, Part 4: *R. Kreher* and *G. Jäger*, Z. Naturforsch. *20b*, 1131 (1965). — Part 3: *R. Kreher* and *G. Jäger*, Angew. Chem. *77*, 963 (1965); Angew. Chem. internat. Edit. *4*, 952 (1965); *R. Kreher*, lecture to the Chemiedozenten-Tagung 1970 in Köln.

[2] Under similar conditions, the isoelectronic diazo compounds *(2)* investigated surprisingly exhibit different behavior. Cf. *G. Wagner*, Diploma Thesis, Technische Hochschule Darmstadt 1971.

[3] *P. G. Gassman*, Accounts of Chem. Res. *3*, 26 (1970).

[4] The use of nitrosyl tetrafluoroborate for the production of carbonium ions from organic azides has been described by *M. P. Doyle* and *W. Wierenga*, J. Amer. Chem. Soc. *92*, 4999 (1970).

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New Impetus for Food Research Under the Auspices of the Federal Ministry for Food, Agriculture, and Forestry (BML)

By *Felix Krusen*[*]

Of the 16 Federal Research Institutes under the BML, eight are concerned exclusively with food research (meat, fish, milk, fats, cereals, food preservation, quality of plant products, domestic science). As a result of reorganization of BML research, three special departments have been created with senates of leading scientists, the staff of each department comprising 25% scientific personnel. The department "Food Research and Food Technology", which covers the eight institutes mentioned above, has grouped the research programs of the different institutes under five headings: maintenance and improvement of food quality, progress in food technology, consumer-oriented research, economic problems, and fishery research. There are also three main objectives: control of residues, protein production, and improvement of fat quality. The aim is to increase cooperation and to promote joint research among the institutes, in the hope of improving efficiency.

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The Relationship of Trichloromethanesulfenyl Chloride and Related Compounds to Carbonic Acid Chemistry

By *Engelbert Kühle*[*]

An attempt is made to fit trichloromethanesulfenyl chloride ("perchloromethyl mercaptan") $Cl_3C—SCl$, which may be regarded as orthocarbonic acid trichloride sulfenyl chloride, and the sulfenyl chlorides derived from it, such as chlorocarbonylsulfenyl chloride, chlorothiocarbonylsulfenyl chloride, iminochloromethanesulfenyl chloride, and dichloromethanebis(sulfenyl chloride), into a general scheme of carbonic acid chemistry. The relationship of these sulfenyl chlorides with carbonic acid derivatives was examined on the basis of a number of reactions.

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Organolead Compounds $(Y\text{-}C_6H_4)_nPbX_{4-n}$ with Reactive Substituents Y

By *Friedo Huber* and *Eberhard Kunze* (Lecturer)[*]

Compounds R_nPbX_{4-n} (n=4,3,2,1) with R=m-$O_2N—C_6H_4$ were prepared and investigated as model substances for R′=Y—C_6H_4 with Y as a reactive electron-withdrawing substituent. R_4Pb, which cannot be obtained by direct nitration of $(C_6H_5)_4Pb$, can be prepared by introduction of the nitro group into $(C_6H_5)_2Pb(NO_3)$ by treatment with concentrated sulfuric acid [the same method can be used for $(Z_m—C_6H_{5-m})_2Pb(NO_3)_2$ with Z=4-CH_3, 3-CH_3, m=1 and Z=3,5-CH_3, m=2], conversion of the resulting $R_2PbSO_4 \cdot xH_2O$ into R_2PbX_2 (X=Cl, Br) and symmetrization with hydrazine. Mild degradation with bromine leads to R_3PbBr. $RPb(OCO—CH_3)_3$ is prepared by reaction of $Hg(OCO—CH_3)_2$ with $R_2Pb(OCO—CH_3)_2$.

$R_2Pb(OCO—CH_3)_2$ reacts with HBr and $(C_6H_5)_4PBr$ in glacial acetic acid to give $[(C_6H_5)_4P]_2(R_2PbBr_4)$, and with HCl and $(C_6H_5)_4PCl$ in acetone/methanol to give $[(C_6H_5)_4P](R_2PbCl_3)$. The introduction of the nitro groups renders electrophilic attack on the aryl-lead bond more difficult, and the solubilities are considerably altered in some cases.

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Anion-Exchange Behavior of Protactinium and Other Elements in Mixtures of HNO_3, HF, and Organic Solvents

By *H. W. Lagally* (Lecturer), *J. I. Kim*, and *H.-J. Born*[*]

The anion-exchange behavior of protactinium was investigated in several water-miscible organic solvents containing HNO_3 and HF as complexing agents. Solvents with low to high dielectric constants were chosen. The adsorption of uranium, thorium, and other elements in these solutions was also investigated. By variation of the solvent and its concentration in the acid mixture, it is possible to increase the adsorption of the anions in question on the ion exchange resin to the desired degree. The effects of the dielectric constant, the dipole moment, the ionic strength of the solution, *etc.* on the adsorption are discussed. On the basis of these results, possibilities are shown for the separation of protactinium from the other elements, the protactinium remaining stable in the mixtures containing HF.

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Reaction of Silicon Nitride with Oxygen

By *I. Fränz* and *W. Langheinrich* (Lecturer)[*]

When thin layers of vitreous silicon nitride, such as can be deposited *e. g.* on silicon by reaction of silane with ammonia, are heated in oxygen, silicon dioxide is formed as a thin vitreous layer with a sharp boundary between the two phases in accordance with the equation

$$Si_3N_4 + 3\,O_2 \rightarrow 3\,SiO_2 + 2\,N_2$$

For greater thickness of the SiO_2 layers formed, *i. e.* when the growth process has become stationary, a parabolic law of the form

$$x^2 = B \cdot t$$

where x is the thickness of the SiO_2 layer formed, t is the oxidation time, and B is a temperature-dependent constant, is valid for heating in dry as well as in moist oxygen.

The formation of SiO_2 from silicon nitride is much slower than the thermal oxidation of silicon, which also follows a parabolic law for large layer thicknesses. This is probably due to the fact that the equilibrium concentration of the oxidant in the oxide is influenced by nitrogen which is produced in the interface reaction and which diffuses to the surface.

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Detection of Staphylococcus Enterotoxins with the Aid of a New "Micro-Slide Kit" for Immune Diffusion

By *H. J. Langner*[*]

There is a need for increasing sensitivity of detection methods in analytical chemistry. This also applies to the detection of macromolecular natural products such as proteins. If such substances can be isolated in a highly purified form and used for the preparation of antiserums, immune diffusion offers an extremely sensitive and specific method of detection and determination. In immune diffusion on the micro scale, however, all the important analytical parameters must be accurately standardized. On the other hand, nearly every laboratory has its own individual procedures for this method. A complete outfit[**], including reagents, for "micro-slide immune diffusion", in which all the parts are rigorously standardized, and which allows the very simple execution of both qualitative and quantitative protein determinations, *e. g.* detection of staphylococcus enterotoxins, milk protein, soybean protein, and egg protein in other foods, in microbiological nutrient solutions, or in human examination material, is proposed in this lecture.

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[**] Obtainable from SERVA, Heidelberg (Germany) and GALLARD-Schlesinger, New York (USA).

Separation of Fission Inert Gases from Combustion Waste Gases from High-Temperature Fuel Elements by Washing with Liquid Carbon Dioxide

By *Manfred Laser* (Lecturer) and *Holger Beaujean*[*]

The separation by washing and subsequent rectification is carried out in a compact apparatus designed for a combustion gas throughput of 1 Nm^3/h. The columns have the following dimensions:

Wash column: height 2500 mm, diameter 43 mm, packing: wire mesh rings with web 6 × 6 mm.

Rectifying column: total height 1200 mm, of which the rectifying section accounts for 450 mm and the stripping section for 750 mm; packing: wire helices, 4 × 4 mm.

Measurements on the equilibrium between Kr and CO_2 showed that the solubility is better than the calculated value at Kr contents ≤ 1000 ppm. This leads to the relatively favorable gas/solvent ratio of 80 in the wash column and facilitates the concentration of krypton in the rectifying section of the rectifying column.

The solubility coefficient for Kr is 0.00715 at 25 °C.

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Possibilities in Preparative Organometallic Electrochemistry

By *Herbert Lehmkuhl* (Lecturer), *Wolfgang Leuchte, Edo Janssen, Klaus Mehler, Siegfried Kintopf*, and *Wilhelm Eisenbach*[*]

Organometallic complex compounds of main group metals (Al) and transition metals with aromatic, olefinic, or cycloolefinic hydrocarbons as ligands can be synthesized by electrochemical reduction of suitable, readily obtainable metal compounds (chlorides, acetylacetonates, alkyls, *etc.*) in the presence of the ligands. The electrochemical systems consist of the two components of the desired complex, an organic, usually aprotic solvent (pyridine, THF, DMF, dimethoxyethane), and a suitable conducting salt (lithium halide, tetraalkylammonium halide, alkali metal tetraalkylaluminate, *etc.*). Depending on the anode process coupled with the reduction at the cathode, one thus achieves an electrochemical synthesis from compact metal (anode) and ligand:

$$M\,(\text{Anode}) + \text{Lig} \rightarrow [M \ldots . \text{Lig}]$$

This synthesis has been achieved for cyclooctatetraenenickel(0), bis-cyclooctatetraenenickel(0), and bis-cyclooctatetraeneiron(0).

If the complex formed at the cathode is oxidized more readily than the anode metal, the electrode compartments must be separated by diaphragms, or a more readily oxidizable metal may be used as the anode. Aluminum has proved particularly suitable for this purpose. The overall electrochemical reaction is then given by:

$$M^{\oplus} + M'\,(\text{Anode}) + \text{Lig} \rightarrow M'^{\oplus} + [M \ldots . \text{Lig}]$$

$$M' = \tfrac{1}{3}\,Al$$

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This general case has been verified in the syntheses of cyclooctatetraenetitanium chloride, bis-cyclooctatetraenezirconium dichloride, π-cyclooctenylcobalt-1,5-cyclooctadiene, bis-1,5-cyclooctadienenickel, and 1,5,9-cyclododecatrienenickel.

4-Bromo-5-cyclohexene-1,2,3-triol as a Specific Inactivator for the α-Glucosidases of Yeast (Saccharomyces cerevisiae)

By *Günter Legler* (Lecturer) and *Wolfgang Lotz*[*]

The reaction of α-glucosidases with all-*trans*-4-bromo-5-cyclohexene-1,2,3-triol (bromoconduritol) leads to irreversible inhibition. Investigation of the inactivation reaction with an enzyme isolated in pure form from brewers' yeast showed second order kinetics at concentrations around 10^{-6} mole/l ($k = 8.8 \times 10^4$ $mole^{-1}$ l min^{-1} at 25 °C and pH = 6.0). Substrate or competitive inhibitors reduce the reaction rate, pointing to an attack on the active center. The enzyme has two SH groups, one of which is essential. After inactivation with bromoconduritol, only 0.5 SH/mole was detectable; however, the SH groups become fully accessible again on denaturation. Reaction with a histidine residue is assumed from the amino acid analysis. The pH dependence of the inactivation reaction and the behavior of the epoxide obtained from bromoconduritol indicate that the bromoconduritol is converted into the epoxide on the enzyme before the reaction.

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The Solvolysis of 1-Methyl-2-adamantyl Compounds (Influence of β-Methyl Substitution on the Solvolysis of Secondary Compounds)

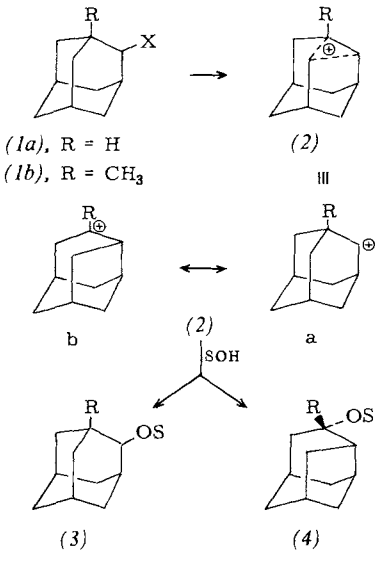
By *Dieter Lenoir* (Lecturer) and *Paul v. R. Schleyer*[*]

The solvolysis of unsubstituted 2-adamantyl compounds *(1)*, R = H, X = tosyloxy or bromine, was chosen as a model for a limiting solvolysis mechanism (k_c mechanism) of secondary substrates. Whereas solvent assistance (k_s mechanism) could be ruled out, the question of the magnitude of a possible anchimeric component (k_Δ) was particularly interesting.

The effect of a carbonium ion-stabilizing methyl group on C-1 on the nature of the secondary ion (2) was therefore investigated. The rate of solvolysis of the substituted compounds *(1)*, R = CH_3, X = tosyloxy or bromine, is 35 times that of the unsubstituted compounds *(1)*, R = H, X = tosyloxy or bromine at 25 °C. Whereas only 0.4% of the rearrangement product *(4)* with R = H, OS = acetate is formed in the kinetically controlled solvolysis of the unsubstituted compound *(1a)*, X = tosyloxy, in glacial acetic acid, the component of the rearrangement product *(4)* with R = CH_3, OS = OH is increased to 30% in the solvolysis of *(1b)* in 60% acetone.

It is clear from these kinetic findings, particularly the formation of the rearrangement product with a uniform

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(1a), R = H
(1b), R = CH_3

(2)

(3)

(4)

4-*exo*-protoadamantane structure, that the ion *(2)* with R = H is only very weakly bridged, whereas the ion *(2)* with R = CH_3 has a considerable proportion of bridged character. The difference between the energies of the two canonical forms a and b is reduced as a result of compensation of electronic effects by strain effects only in the substituted ion.

The special stability of the ion *(2)* with R = CH_3 is also confirmed by the result of the solvolysis of the 4-epimeric 4-methylprotoadamantyl 3,5-dinitrobenzoate in 60% acetone; with kinetic control, both substrates give a product ratio similar to that obtained from *(1b)*, so that the ion *(2)* is a common intermediate for all three substrates.

The application of the linear free energy relation shows that the protoadamantane system is richer in energy by about 11 kcal/mole than the adamantane system; this value agrees satisfactorily with the results calculated from conformational analysis.

Ternary Chromium Sulfides

By *H. D. Lutz* (lecturer), *K.-H. Bertram*, *R.-A. Becker*, and *W. Becker*[*]

In the reaction (950°C) of CrS (NiAs defect structure) with transition metal sulfides having the formula MS (M = Mn, Fe, Co, Ni, Cu, and Zn), the very strong reducing power of "chromium(II) sulfide" leads to the formation of higher sulfides of chromium ($FeCr_2S_4$ cubic or monoclinic, $CoCr_2S_4$ cubic, $Ni_xCr_{3-x}S_4$ monoclinic). The sulfides used are thus reduced to the metals (Fe, Co, Ni) or subsulfides (Ni_3S_2). No reduction is observed in the systems CuS—CrS (formation of rhombohedral $CuCrS_2$), MnS—CrS, and ZnS—CrS. The desired stabilization of a chromium sulfide that crystallizes in the undistorted NiAs type by solid solution formation with NiS, CoS, or FeS could not be achieved.

To clarify the conditions for the transformation of the spinel lattice of the ternary chromium sulfides MCr_2S_4 (M = Mn, Fe, Co, Cu, and Zn) into the monoclinic NiAs defect structure of $NiCr_2S_4$, the mutual miscibility was investigated in the systems $CoCr_2S_4$—$NiCr_2S_4$ (spinel → $Co_{0.81}Ni_{0.19}Cr_2S_4$) and $CuCr_2S_4$—$NiCr_2S_4$ (spinel → $Cu_{0.74}Ni_{0.26}Cr_2S_4$). In the system $CoCr_2S_4$—$CuCr_2S_4$, solid solution formation was observed between the metallically conducting copper chrome thio-spinel and the semiconducting cobalt compound in all proportions. However, the Vegard rule is not satisfied.

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Sulfane Derivatives of Hydrazine

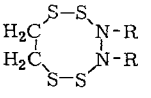
By *Karl-Heinz Linke* (lecturer), *Herbert Lingmann*, *Rudolf Bimczok*, *Hans Jürgen Göhausen*, and *Dietmar Skupin*[*]

Whereas hydrazine is oxidized to nitrogen by chlorosulfanes, a series of cyclic and open-chain sulfane derivatives of hydrazine have been synthesized by reaction of esters of hydrazinedicarboxylic acid or dimethylhydrazine with chlorosulfanes:

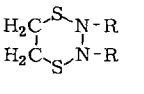


(1a)-(1c)

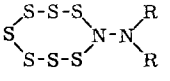
(2a), *(2b)*



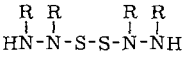
(3a)



(4a)

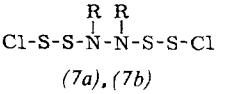


(5a)



(6a), *(6b)*

(*a*), R = $CO_2C_2H_5$
(*b*), R = $CO_2C(CH_3)_3$
(*c*), R = CH_3



(7a), *(7b)*

(6a) is also formed in high yields by addition of disulfane to diethyl azodicarboxylate.

Attempts to remove the ester groups from the heterocyclic compounds *(1b)* and *(2b)* by acidolysis or pyrolysis failed to lead to the isolation of unsubstituted sulfur-nitrogen rings containing nitrogen-nitrogen bonds.

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Thermodynamic and Kinetic Aspects of the Synthesis of New Forms of Carbon

By *H. Lydtin*[*]

The novel forms of elementary carbon, such as "highly oriented pyrographite" and "vitreous carbon", are products of special preparation methods. In these methods, the carbon formation is forced to occur either by condensation of carbon from the gas phase on substrate surfaces or by pyrolysis of suitable organic substances in the solid state.

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Both methods are based on the thermal instability of organic carbon compounds. Apart from hydrocarbons, which are the most commonly used materials in practice, other systems that may be considered on thermodynamic grounds for the deposition of carbon from the gas phase include C/S, C/Cl, and C/O.

The molecular mechanisms of carbon formation differ in the two methods. In the gas-phase deposition, the desired deposition of carbon takes place either by direct condensation of atomic carbon or by the decomposition of molecules containing carbon on the surface. Depending on the temperature and pressure, complications can arise from cluster formation in the gas phase or from inadequate thermal accommodation on the surface of the solid. In the pyrolysis of solids, the carbon formation depends on simultaneous decomposition and diffusion processes in the initial and intermediate stages of the material used. The structure of the final product depends not only on the starting materials but also on the competition between production (decomposition) and elimination (diffusion) of the cleavage products.

By suitable choice of the starting material, the preparation method, and the preparation conditions, it is possible to adjust a number of properties in the final product over wide ranges. This fact, together with good chemical and thermal stability, is the basis of the wide range of possible applications and uses of these modern materials.

The Binding of Volatile Carbonyl Compounds to Food Components

By *H. G. Maier*[*]

The adsorption and desorption of the vapors of aldehydes (C_3 and C_6 alkanals and alkenals, some aromatic) and ketones (C_3—C_5 alkanones, biacetyl, camphor) to food components that are poor in water at room temperature has been investigated by IR-spectroscopic and gas-chromatographic methods. Ketones are adsorbed only in small quantities in the absence of water, while adsorption by macromolecular substances improves with increasing water content. Rapid drying then leads to the formation of nonstoichiometric inclusion compounds. The quantities adsorbed decrease with the molecular size. Aldehydes are usually bound in a similar manner and in similar quantities. The physical adsorption on water-free solids is often greater. Chemical reaction occurs with some low molecular weight solids, and leads *e.g.* in the case of cysteine and urea to bonding that is reversible in the presence of water.

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Enumeration, Identification, and Significance of Staphylococci in Dried Soups and Their Raw Materials

By *R. S. Moussa* and *J. C. de Man* (lecturer)[*]

Of all the culture media suggested for the enumeration and identification of pathogenic staphylococci, that most commonly used in food laboratories is the Baird-Parker medium. The advantages and some limitations of this medium were discussed, and the results obtained with other culture media were compared with those obtained with the Baird-Parker medium. When Baird-Parker culture medium is used for the enumeration of *Staphylococcus aureus* in dried soups and their raw materials, a large number of the colonies that develop must be tested for coagulase and/or deoxyribonuclease-production, and occasionally for ability to produce enterotoxin.

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Influence of Conformation on the Stereochemical Course of Hot Substitution Reactions in Diastereomeric Haloalkanes

By *H. J. Machulla* (lecturer), *L. Vasaros*, and *Gerhard Stöcklin*[*]

The question of the mechanism of hot substitution reactions with high translational energies (eV range) was reinvestigated for diastereomeric 1,2-dichloro-1,2-difluoroethanes and 2,3-dihalobutanes in the light of conformational analysis. In the liquid phase, the replacement of hydrogen by recoil tritium, and to a greater degree the replacement of halogen by recoil halogen atoms, can also take place with inversion of configuration under favorable steric conditions. By comparative IR-spectroscopic conformational analysis and radiochemical yield determination in solvents of different dielectric constants, it was possible to show that the stereochemical course is strongly dependent on the conformation of the rotational isomers, and can be varied within a wide range (*e.g.* 30 to 85% retention of configuration in the case of recoil chlorine in 2,3-dichlorobutane) by changing of the equilibrium concentration of the conformers.

This conformational effect exhibits a new characteristic feature of hot one-step substitution and indicates that these reactions may also proceed as concerted processes *via* a collision complex that is long-lived as compared to molecular vibration periods.

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Search for "Solar Wind" Rhenium in Moon Samples

By *U. Herpers*, *R. Michel* (lecturer), and *W. Herr*[*]

Since the natural β-radioactive ^{187}Re ($E_\beta \approx 2$ keV) in the interior of the sun possibly suffers a faster "bound-state" β^--decay—as was predicted some years ago—one would expect this nuclide to be deficient in the "solar wind". The composition of the latter shows that all elements are present with almost cosmic abundances. Since lunar materials was available we had the chance to study the composition of the captured "solar wind" rhenium. Therefore, we measured the isotopic abundance of ^{185}Re and ^{187}Re by neutron activation techniques.

After an intense neutron bombardment suitable preparations were subjected to γ spectroscopy with a 20 cm^3

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Ge(Li)-detector. The isotope ratio was checked by comparing the 137 keV γ line of ^{186}Re with the 155 keV γ line of ^{188}Re. Lunar rocks gave Re contents between 0.2×10^{-10} and 0.9×10^{-10} g/g, which roughly correspond to those of achondritic meteorites. The soil samples were found to be considerably richer (70×10^{-10} to 110×10^{-10} g/g for Apollo 11 regolith and 6×10^{-10} g/g for Apollo 12 regolith). In rocks Re was found—contrary to expectation—to be slightly enriched in ^{187}Re.

This effect is believed to be due to the neutron capture reaction $^{186}W(n,\gamma)^{187}W \xrightarrow{\beta^-} {}^{187}Re$. The possibility of deriving thermal and epithermal neutron fluxes on the lunar surface by the Re-isotope anomaly was discussed.

Fast-Drying Binder Based on Dehydrated, Epoxidized Linseed Oil in Theory and Practice

By *J. D. von Mikusch-Buchberg* (lecturer, Part I) and *E. W. Trautschold* (lecturer, Part II)[*]

Varnish and paint binders that dry rapidly to hard films are obtained from linseed oil by (a) partial epoxidation, (b) complete esterification of the epoxy oil with unsaturated fatty acids, and (c) thermal cleavage of the estolide with formation of new double bonds. Since the removal of the fatty acids is incomplete, the stand oil-like product has an increased functionality. Drying proceeds with the typical characteristics of conjugated unsaturated oils, but completely tack-free films are formed. A detailed discussion of the individual process steps (Part I) was followed by a report on the results of outdoor weathering and other practical tests (Part II).

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Chemical Consequences of the $^{185}Re(n,\gamma)^{186}Re$ Nuclear Process in the Double Salt $K_2ReF_6 \cdot KCl$

By *Horst Müller* (lecturer)[*] and *Siegfried Abberger*[**]

The hitherto unknown double salt $K_2ReF_6 \cdot KCl$ can be obtained from a solution of the components. It crystallizes tetragonally with $a = 12.009$ and $c = 11.847$ Å. Model considerations suggest that its structure is very similar to that of $(NH_4)_3[SiF_6]F$. It should thus be built up from a succession of ReF_6^{2-} and Cl^- in the c direction, with K^+ scattered between the layers.

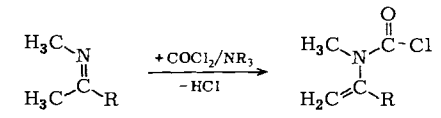
The ^{186}Re recoil atoms formed as a result of neutron capture, which have a recoil energy of about 70 eV, react in the lattice to give mixed chlorofluororhenates(IV) $^{186}ReCl_nF_{6-n}^{2-}$. The two forms $^{186}ReCl_3F_3^{2-}$ and $^{186}ReCl_4F_2^{2-}$ are formed only in very small quantities, and the two forms $^{186}ReCl_5F^{2-}$ and $^{186}ReCl_6^{2-}$ are totally absent. The possibility of using these results as a basis for conclusions regarding the degree of distortion of the lattice as a result of the recoil process was discussed.

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New Carbamoyl Chlorides by Phosgenation of Lactim Ethers, Imido Esters, and Schiff Bases and by Chlorination of *N,N*-Dimethylcarbamoyl Chloride

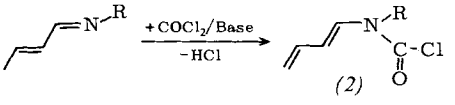
By *Albrecht Müller* (lecturer), *Hans Kiefer*, *Karl-Heinz König*, *Horst Pommer*, and *Bernd Zeeh*[*]

The reaction of azomethines, lactim ethers, and imido esters with phosgene in the presence of tertiary amines leads in good yields to hitherto unobtainable α,β-unsaturated carbamoyl chlorides, *e.g. (1)*. These reactions are based on a general synthetic principle that can also be applied to other reactive acylating agents, such as chloroacetyl chloride and acetyl chloride.



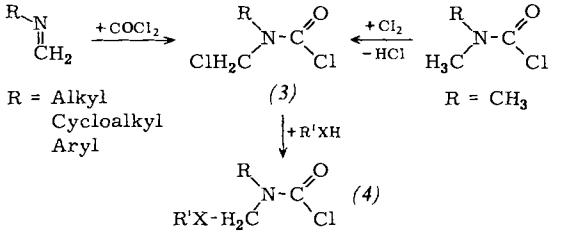
R = H, OCH_3 *(1)*

α,β-Unsaturated azomethines can be converted in the same way into the corresponding butadienylcarbamoyl chlorides *(2)*:



(2)

In the absence of bases, it is possible to isolate the α-chloroalkylcarbamoyl chlorides, which tend to undergo dehydrochlorination. Azomethines of formaldehyde, on the other hand, yield stable chloromethylcarbamoyl chlorides, which are also obtainable *e.g.* by chlorination of *N,N*-dimethylcarbamoyl chloride:



R = Alkyl, Cycloalkyl, Aryl *(3)* $R = CH_3$ *(4)*

The selective substitution of *(3)* with various nucleophiles R'XH (X = O, S, OAc, SAc) with formation of *(4)* was described.

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Thermal Aldol Reactions Between Ketones and Aldehydes

By *Herbert Müller* (lecturer), *Georg Klotmann*, and *Hermann Overwien*[*]

Little attention has been paid so far to thermally initiated aldol condensations between ketones and aldehydes. In many cases, however, these reactions proceed much

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more selectively than the catalytic reactions, provided that the correct reaction conditions are strictly maintained.

The reaction products obtained are identical with those of the catalytic condensation. The primary products are keto alcohols, which may be dehydrated to form unsaturated ketones under the drastic reaction conditions.

The synthesis proceeds surprisingly smoothly with aldehydes substituted in the α position by alkyl or aryl groups and with formaldehyde. The structure of the ketones, on the other hand, has little effect on the course of the reaction.

The reaction temperatures required are mainly determined by the aldehydes. For simple adehydes they are between 200 and 300 °C. They can be reduced by 100 °C by the use of aldehydes with electron-attracting groups in the α position. An example of this is the condensation of glyoxylic acid with acetone, which gives acetylacrylic acid in high yields.

Inverse-Voltammetric Determination of Traces of Antimony after Separation of the Matrix by Various Methods

By *Hans Monien* (lecturer), *Doris Bohn* and *Peter Jacob*[*]

For the determination of approximately 0.5 to 5 ppm of antimony in metallic iron, copper, and bismuth, the matrix is separated by extraction, by column chromatography, and by potentiostatic electrolysis. With the extraction of iron or copper, the complete analysis takes one hour. The antimony content of the iron is 0.54 ppm, the relative standard deviation of the results being 0.12. The copper analyzed contains 3.8 ppm of antimony (relative standard deviation 0.03). The separation of iron or copper by column chromatography takes two hours. The results of the analyses agree with those given above. The relative standard deviation in this determination is 0.06. With separation of copper by potentiostatic electrolysis, an analysis takes 90 minutes.

In all three separation methods, for sample weights of between 0.2 and 1 g, only a few minutes are required for the dissolution process and the preparation of the solution for separation of the matrix. About half of the time indicated is taken up by the separation, and the remainder by the preparation of the solution for the voltammetric determination. Direct determination of 2.0 ppm of antimony is possible only in bismuth. The antimony determinations are carried out with a carbon paste electrode by the addition method.

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Investigations on Neutron-Induced Radiation Damage in KCl Single Crystals

By *M. Müller*[*]

The mobility of argon that can be formed by the (n,p) nuclear reaction, which is very strongly dependent on the irradiation defect concentration[1], was used as an indicator of radiation damage. An activation energy of $\Delta H = 1.9$ eV was found for the annealing of the radiation damage, which occurred preferentially on the surface of the single crystals. It was therefore concluded that the neutron irradiation probably leads to the formation of small vacancy clusters, which are broken down at the surface on heating.

The extent to which an interpretation of the gas release kinetics is still possible was investigated[2]. A homogeneous defect concentration has been assumed in the past, but this is no longer present because of the healing. It was found that the diffusion coefficients must be discussed as a function of position and time.

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[1] *F. Felix*, HMI-B-93, Juni 1970; *P. Schmeling*, J. Phys. Chem. Sol. *28*, 1185 (1967); Phys. Stat. Sol. *11*, 175 (1965).

[2] *M. J. Norgett* and *A. B. Lidiard*, IAEA-SM-120/A-4 Wien 1969; *H. Gaus*, Z. Naturforsch. *20a*, 1298 (1965).

Volatilization of Fission-Product Chlorides from Solid UCl_4

By *Bernd Neidhart* (lecturer), *Knut Bächmann*, *Silke Kubny*, *K. H. Lieser*, and *Elke Stoll*[*]

For the development of targets for on-line experiments on nuclear reactors, UCl_4 and mixtures of $^{235}UCl_4$ with KCl, $SrCl_2$, and YCl_3 were irradiated in the reactor, and the volatilization of chlorides of the fission products Zr, Nb, Mo, Tc, and Te was investigated as a function of the temperature and of the matrix. Between 30% (Zr) and 80% (Tc) of the fission products formed can be volatilized from UCl_4 as the chlorides at about 400 °C. The delay times in the target are 15 to 40 s. Only a slight improvement results when the temperature is raised to 600 °C (m.p. of UCl_4). A clean separation of the products cannot be achieved by variation of the temperature. When $^{235}UCl_4$ is mixed *e.g.* with $SrCl_2$ in a ratio of 1:30, Tc leaves the target at 550 °C and Te at 680 °C, while the other elements are retained up to 800 °C. KCl and YCl_3 show similar effects. With a suitable choice of the matrix and of the temperature, Tc and Te can be separated from the other fission products, and Tc can even be separated from Te.

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Gallium Arsenide Whisker Growth by the VLS Mechanism

By *W. Just*, *J. J. Nickl* (lecturer), and *H.-J. Kaiser*[*]

The growth of gallium arsenide crystals in the system $Ga—AsCl_3—H_2$ was investigated with quartz and GaAs substrates coated with liquid gallium to induce whisker growth by the VLS mechanism. The morphology of the GaAs crystals is largely determined by the temperature. Whisker growth was observed between 550 and 680 °C. In the lower temperature range (< 640 °C), only ⟨111⟩-oriented needles twinned perpendicular to the growth direction were found. Only ⟨112⟩ blades twinned parallel to the growth direction grew in a higher temperature range (> 640 °C).

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A new type of whisker, rosette whiskers, was found in the region of needle growth.

The same temperature dependence of the whisker morphology is observed when the gallium is replaced in the reaction system by CH_3GaCl_2 or $GaCl_3$.

The temperature dependence of the electric properties of the GaAs whiskers is comparable with that of epitaxially deposited GaAs layers produced under similar conditions.

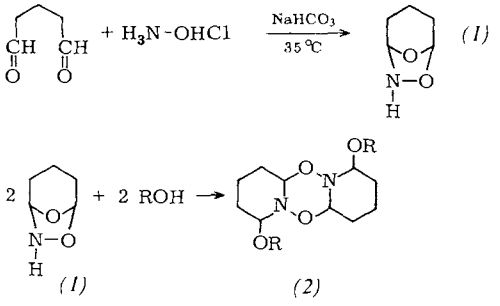
New Reaction Products from Glutaraldehyde, Hydroxylamine, and Alcohols

By *Gerd Eikelmann, Werner Heimberger, Gerhard Nonnenmacher* (lecturer), and *Wolfgang Weigert*[*]

A uniform reaction product is obtained from glutaraldehyde and 1 mole of hydroxylammonium chloride only under certain conditions. If a molar solution of hydroxylammonium chloride is added dropwise to an aqueous solution of glutaraldehyde at 35 °C over a period of 60 min, the acid liberated being intercepted by acid acceptors, a colorless product, m.p. = 169—171 °C, is obtained in more than 80% yield; on the basis of the element analysis, and the IR and mass spectra, this product is assumed to have the structure *(1)*. The product *(1)* can be converted into the dioxime by reaction with further hydroxylamine.

If *(1)* is heated for a short time with methanol or allowed to stand for a few hours at room temperature in suspension in methanol, thorough drying and repeated recrystallization from CH_2Cl_2 leads to more than 80% yield of a substance having m.p. = 155—160 °C, whose IR, NMR, and mass spectra indicate the structure *(2)*. In a similar way the reaction of *(1)* with ethanol leads to an ethoxy compound of structure *(2)*.

Unlike *(1)*, which is insoluble in water and in the common organic solvents, *(2)* dissolves readily in all lipophilic solvents.



R = CH_3, CH_2CH_3

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A Vector Scheme for Separation Processes

By *Holm Pauschmann*[*]

All processes for the separation of matter on the basis of differences in migration velocities are traced back to combinations of three elements:

1. migrations in which the individual types of particles move with different velocities,

2. displacements that influence all types of particles to the same extent,

3. gradients that modify migrations or displacements.

Because of their direction in space, these elements are vectors, from which it is possible to develop a theoretical "building block system" that can be used for the interpretation of existing separation processes and for the development of new processes. Some examples of new or possible processes were described, and the conclusions collected into fundamental rules.

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Dependence of the Enzyme Mechanism on Allosteric Effectors in the Case of Isocitrate Dehydrogenase

By *Dieter Palm* (lecturer) and *H. Katzendobler*[*]

The dependence of the isotope effect of *threo*-D_s-[2-^{3}H]-isocitrate and of the activation energies on the substrate concentrations and the presence of the effector 5'-AMP in the reaction of isocitrate dehydrogenase from yeast indicated a dependence of the enzyme mechanism on the ligands. A "random order rapid equilibrium mechanism" at low NAD concentrations is replaced by a "compulsory ordered mechanism" at high NAD concentrations or in the presence of 5'-AMP. This showed that pure allosteric K systems (classification of *Monod, Wyman*, and *Changeux* —different affinity for different enzyme states) probably do not exist. As in the example described, a conformation of the binding site(s) that leads to a different affinity also influences the kinetic behavior of the enzyme.

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Electron Spin Resonance of ^{99}Tc(IV) in $K_2[PtF_6]$ and SnO_2

By *H. H. Pieper* (lecturer), *W. Krasser*, and *K. Schwochau*[*]

The ESR hyperfine structure spectra of ^{99}Tc(IV) in $K_2[PtF_6]$ and SnO_2 single crystals were measured in the Q band at 77 °K and 4.2 °K resp., and depending on the crystal orientation. The spectrum of the fluoro complex with 10 HFS lines corresponding to the nuclear spin 9/2 ħ of Tc-99, shows strong anisotropy in agreement with results of vibrational spectroscopy, which is, to a first approximation, attributable to a trigonal distortion of the octahedral ligand field.

The line-rich, orientation-dependent SHFS spectrum of doped SnO_2 single crystals can be explained by the interaction of the Tc(IV) with the adjacent Sn atoms. The term splitting of the Tc(IV) is due to the nearly octahedral ligand field of the oxygen atoms and the adjacent Sn atoms.

Both spectra were described with suitable spin-Hamilton operators, and the constants were calculated.

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Binary Compounds of Boron with Main Group V Elements with Retention of Basic Icosahedral Frameworks: Tetragonal Boron Nitride and Rhombohedral Boron Phosphide

By *Klaus Ploog* (lecturer), *Peter Rauh*, *Wolfgang Stoeger*, and *Herbert Schmidt*[*]

In an experimental apparatus of new design, we were able to prepare a tetragonal boron nitride having the composition $B_{53}N$ to $B_{28}N$ by pyrolysis of BBr_3—H_2-mixtures and additional N_2 on BN-substrates at 1150 to 1500 °C. With rising preparation temperature, the content of nitrogen in the grown material increases from 2.40 to 4.50 wt.%; the densities increase in the same order from 2.404 to 2.460 g/cm³, and the lattice constants a from 8.79 to 9.02 Å and c from 5.08 to 5.26 Å. The structure of this compound is derived from the lattice of the so called I-tetragonal boron: The basic I-tetragonal framework with four B_{12}-icosahedra and two single B-atoms is preserved, and the N-atoms occupy one or two of the larger tetrahedral holes.

In a similar manner we obtained a rhombohedral boron phosphide having the composition $B_{48}P$ to B_9P by pyrolysis of BBr_3—PBr_3—H_2-mixtures on tantalum wires at 1150 °C. Despite their wide range of compositions, the products are derived from the same basic framework: As in boron carbide $B_{13}C_2$, rhombohedrally linked B_{12}-icosahedra form large elongated cavities in the [111]-direction, in which theoretically five sites per unit cell can be occupied by single B- and/or P-atoms. With rising phosphorus content a three-dimensional lattice expansion is oberved; a increases from 5.83 to 5.99 Å and c from 11.71 to 11.98 Å (rhombohedral: a from 5.15 to 5.29 Å and α from 68.9 to 69.8 Å). The hexagonal a to c ratio remains nearly constant. The question which of the available sites along [111] are occupied by B- or P-atoms depends very strongly on the preparation conditions.

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Low-Yield Nuclear Reactions Induced by Fast Neutrons, Particularly (n,t) Reactions

By *S. M. Qaim* (lecturer), *Robert Wölfle*, and *Gerhard Stöcklin*[*]

Little is known as yet about the systematics of low-yield nuclear reactions induced by fast neutrons, particularly (n,t) processes. However, an accurate knowledge of these reactions is of practical interest in connection with the evaluation of undesirable production of tritium in high-flux reactors and for the planning of future fusion reactors. Using radiochemical methods in conjunction with γ-spectrometric, γ,γ-coincidence, and low-level measuring techniques, the cross sections for (n,t) reactions were determined for ^{89}Y and ^{204}Pb with very fast reactor neutrons (> 10 MeV), for ^{50}Cr, ^{54}Fe, ^{64}Zn, ^{92}Mo, ^{139}La, and ^{197}Au with 14.7 MeV neutrons, and for ^{24}Mg, ^{50}Cr, ^{56}Fe, ^{58}Ni, ^{90}Zr, ^{112}Sn, ^{120}Te, ^{133}Cs, ^{197}Au, and ^{204}Pb with approximately 25 MeV neutrons. In addition to the product nuclei, tritium was also separated and measured in some cases. The dependence of the $\sigma(n,t)$ values on the nuclear charge Z of the target for $Z > 10$ shows a maximum at about $Z = 26$, as in the case of the (n,p) reactions. The expected dependence on the relative neutron excess $(N-Z/A)$ is observed for the elements with $Z > 22$, with no indication of shell effects.

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Photochemical Intermediates in Organic Synthesis

By *Horst Prinzbach*[*]

Norbornadienes and 7-methylene, 7-oxa, or 7-aza derivatives are converted into the tetracycles by a (very probably two-step) cycloaddition on *direct* photoexcitation. The high energy content of these photoproducts, which are mostly kinetically very stable, can be utilized for numerous valuable reactions. Isomerizations of the type $2\sigma \rightarrow 2\pi$ and $3\sigma \rightarrow 3\pi$ are often quantitative, and yield *e.g.* specifically substituted heterotropilidenes; additional isomerization pathways are opened up by metal catalysts. Ionic additions to the σ skeleton are largely stereoselective. Reactions with a series of "bishomodienophilic" reagents result in generally stereospecific cycloadditions in positions 1,5 2,4 or 1,4. The behavior of the norbornadienes and of the 7-hetero analogs on *sensitized* photolysis is not uniform. Nevertheless, 6-hydroxyfulvenes and 6-aminofulvenes can be obtained in reasonable yields in this way.

Intramolecular photochemical $[2\pi+2\sigma]$ cycloadditions in substrates such as cyclopropanorbornene, monohomobarrelenes, and bishomobarrelenes, as well as in additionally bridged systems, proceed with preparatively satisfactory results when the steric conditions are suitable. Photoisomerizations of this type can occasionally also be achieved on replacement of the cyclopropane ring by an oxirane or aziridine ring. The *cis, cis, cis-* and *cis, cis, trans*-trishomobenzene products and the bridged systems of the "mitrane" type are particularly interesting here.

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The Pesticide Problem in Water Pollution

By *K.-E. Quentin*[*]

About 40% of the water requirements in the German Federal Republic is supplied directly or indirectly from surface water (rivers, lakes, dams), which is contaminated to a greater or lesser degree by its environment. One of the current pollution problems is concerned with the occurrence, behavior, and removal of pesticides. The small quantities of pesticide present in water contaminated with a wide variety of substances require special methods of sampling and quantitative determination, which were briefly described. Methods that rapidly indicate any danger to water are becoming increasingly important. Pesticide studies in this connection have been concerned with the determination of total contents of insecticidal esters of phosphoric acid and carbamates by enzymatic test methods, as well as with the adsorption of chlorinated

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hydrocarbons on plastic films suspended in the water. Investigations on the kinetics of the adsorption process have led to new approaches to the simplification and acceleration of pesticide checks.

As far as the behavior of pesticides is concerned, studies have been carried out on the changes undergone by insecticidal esters of phosphoric acid in water, *e.g.* on the rate of hydrolysis of parathion under natural conditions and on its microbiological conversion into aminoparathion. The investigations on the relations between pesticides dissolved in water and those bound to solid material suspended in the water are significant in view of the persistence of chlorinated hydrocarbons and their accumulation in the biological chain. Since the various harmful substances do not occur singly in water, it is difficult to estimate a danger situation. A model was therefore developed for the representation of the toxic summation effect of the harmful substances present; the experimental checking of this model is an important task for the future.

The presence of pesticides in water must also be taken into account in the various processes for the preparation of drinking water. Results of investigations on the ozonization of water under waterworks conditions and on the effect of this measure on pesticides of the chlorinated hydrocarbon group were finally reported.

Possibilities of Fast Liquid Chromatography

By *Dieter Randau*[*]

The aim of fast liquid chromatography is the column-chromatographic separation of a mixture of substances and the simultaneous acquisition of quantitative information about the composition. Instruments with high-pressure pumps and sensitive detectors, as well as injection systems with very low dead volumes, are necessary for this purpose.

Silica gels, glass spheres coated with silica gel, and gels are generally used as chromatographic supports. The separation is strongly influenced by the manner in which the column is packed, by the particle size, by the speed of the mobile phase, by the activity of the support, and by eluent exchange. The possibilities of fast liquid chromatography that exists when these parameters are taken into account were demonstrated.

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Polymer Melts as Viscoelastic Liquids

By *Falko Ramsteiner*[*]

Polymer melts are viscoelastic liquids, the study of which is important to many fields. For example, the chemist can draw conclusions concerning certain molecular parameters of polymers from the rheological data for molten polymers, the physicist can carry on the development of the nonlinear viscoelasticity theory by rheological studies on polymer melts, and the engineer must take the viscoelastic properties into account in the design of processing machineries and in the assessment of the service characteristics of plastic end products.

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At low shear rates, most molten polymers exhibit linear viscoelastic behavior as described by the theory of linear viscoelastic bodies. In this theory, quantitative relations exist between the relaxation, stressing, oscillation, and creep behavior (under both shearing and tensile stresses), which are illustrated by some practical examples. The time-temperature behavior is that of a thermo-rheologically simple body. The elastic and viscous properties reflect the molecular weight and the molecular weight distribution.

At high loading rates, the deformation behavior of molten polymers is strongly nonlinear, as is shown by a strong dependence of the viscosity and elasticity on the nature of the load and the occurrence of normal stresses. Finally, some consequences of this nonlinear behavior with regard to processing were mentioned (melt fracture, secondary flow).

The Acid Metabolism in Grapes

By *Adolf Rapp* (lecturer), *Heinz Steffan*, *Gerhard Kupfer*, and *Herbert Ullemeyer*[*]

The acid content of grapes increases during the growth of the berries, reaches a maximum 5—9 weeks after flowering, and then decreases during the ripening of the berries. The start of the incorporation of sugar into the berries coincides with the time of the maximum acid content.

The individual acids differ in their behavior. The malic acid concentration increases gradually after flowering, passes through a maximum, and decreases again during ripening of the berries. The tartaric acid content, on the other hand, reaches a maximum only 4—7 weeks after flowering, and then remains substantially constant during further development of the berries.

By the use of radioactively labeled malic acid, we were able to show that about 60% of the malic acid was consumed in respiration within 15 hours before the acid maximum (30 °C, dark experiment), and more than 90% after the acid maximum. This high activity in the respiratory CO_2 shows the large extent to which malic acid is used as a respiration substrate in ripening berries. The biological half-life of malic acid is between 8 and 13 hours, depending on the stage of growth or ripening of the berries.

The distribution of the radioactivity in the berries shows that acids, amino acids, and sugars are synthesized from the C structure of malic acid during the entire growth and ripening phase. Tartaric acid, on the other hand, is used only to a small extent in respiration, and the quantity used shows no temperature dependence.

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The Glass State of High Polymers

By *Günther Rehage*[*]

The nature of the glass state of high polymers was discussed. The results of recent volume, specific heat, torsion modulus, thermal conductivity, and NMR measurements were dis-

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cussed in this connection. The measurements were carried out over a wide temperature range in the region of the glass transition temperature. Compressibility measurements were also carried out as a function of pressure up to about 10000 atm. It is concluded from the results of the measurements that the vitrification is a freezing-in process. It is not a second order transition, as is often claimed in the literature. Consequently, the Ehrenfest equations for a second order transition are inapplicable. There is also no indication that a second order transition takes place below the glass temperature, as has been suggested by various authors.

The Importance of Microorganisms in the Production of Foods

By *H. J. Rehm*[*]

For thousands of years, there have been foods that are produced with the aid of microorganisms. There has been a steady increase in the number of such foods as a result of modern technical advances. Microorganisms are involved in the production of a number of conventional foods, particularly leavened bread, wheaten breads, alcoholic beverages, various kinds of sausages, numerous milk products, and a number of pure substances such as acetic acid, lactic acid, citric acid, and vitamin C.

Though the production of the above foods is well known, new microbiological technologies have led to several further developments in the production processes.

In addition to these conventional foods, new foods or new substances used in the food industry are produced microbiologically. These include many enzymes, microbiological proteins from various carbon sources, including protein from algae and mushrooms grown by submerged culture, amino acids, and 5'-nucleotides.

As in the USA, attempts will undoubtedly also be made in the German Federal Republic to introduce microbial foods that are already well known in other parts of the world, *e.g.* in Eastern Asia. These include soybean products such as miso and shoyu, fish products, and many others. Examples are nata, sufu, tempeh, prahoc and gari.

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Novel Trinuclear Polymethinecyanine and Polymethinemerocyanine Dyes

By *Christian Reichardt* (lecturer) and *Werner Mormann*[*]

The three aldehyde groups of formylmalonaldehyde $CH(CHO)_3$, which has recently become obtainable, can be made to react in succession, under suitable reaction conditions, with the heterocyclic *N*-alkylimmonium salts that are common in cyanine chemistry in the sense of a base-catalyzed aldol condensation.

Reaction of formylmalonaldehyde with *N*-alkylimmonium salts in equimolar quantities yields novel, negatively solvatochromic γ-formyltetramethinemerocyanine dyes; the same reaction in a molar ratio of 1:2 leads to the hitherto unknown γ-formylpentamethinecyanine dyes. Symmetrical, trinuclear [2.2.2]heptamethinecyanine dyes are obtainable for the first time by condensation of the two reaction partners in a molar ratio of 1:3. The isolation of the monocondensation and dicondensation products of formylmalonaldehyde also allows the preparation of unsymmetrical, trinuclear [2.2.2]heptamethinecyanine dyes.

These trinuclear cyanine dyes may be regarded as vinylogous, or more generally methine-homologous, guanidinium ions, by analogy with the phenylogous guanidinium ions (aminotriphenylmethane dyes).

The spectral properties of the new dyes were described as a function of structure and solvent together with the results of simple HMO calculations.

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Chemical Determination of Amino End Groups in Polyamide Fibers

By *Volker Rossbach*[*]

The reaction of nylon 6 and nylon 6,6 with 2,4-dinitro-1-fluorobenzene[1] in the homogeneous phase (trifluoroethanol) leads to a polymer whose amino groups are *completely* dinitrophenylated. With dinitrophenyl-oligomers as calibration substances, the reaction is used as a specific photometric method for the determination of amino end groups. Its reproducibility is similar to that of the potentiometric method. UV spectroscopic studies on model substances (dinitrophenylamines) and on the methylated polymer show that the new analytical method also allows the differentiation of primary and secondary amino groups and their determination in the presence of each other. A related topic is the detection of heat damage in polyamides. Heat treatment leads to the formation of basic groups, which are detected spectroscopically as the dinitrophenyl derivatives. Another application of the dinitrophenyl method is the difference analysis of fibers dyed with reactive dyes. Thus for Remazol Brilliant Blue R® (vinyl sulfone dye), it is found that about 50% of the amino end groups have reacted.

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[1] *H. Zahn* and *P. Rathgeber*, Melliand Textilber. *34*, 749 (1953).

Pulse Radiolysis in the Gas Phase: the Formation of the Azide Radical in Pure Nitrogen and in Nitrogen Containing Additives

By *E. P. Röth* (lecturer), *J. W. Dreyer*, and *D. Perner*[*]

On irradiation of nitrogen at a pressure of 1—3 atm with fast electrons (600 kV), the azide radical is formed as an intermediate. The yield and formation of N_3 in the electronic ground state $^2\Pi_g$ was measured by kinetic absorption spectroscopy.

In pure nitrogen, the formation of the azide radical can be described by the rate constants of two consecutive reac-

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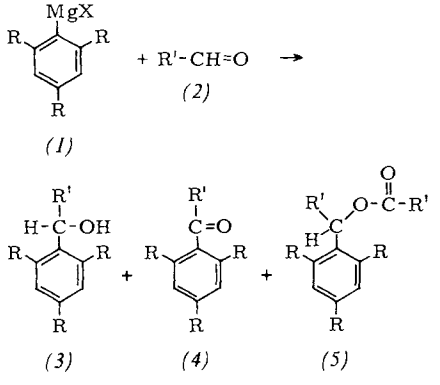
tions. The 100 eV yield increases with the nitrogen pressure, and is approximately 0.2 at 3 atm. The presence of small quantities of, for example, ammonia or cyclopropane leads to much faster formation of N_3. The 100 eV yield is 1.1 in a mixture of 7 torr of cyclopropane in 3 atm of nitrogen.

The formation of N_3 in pure nitrogen is attributed to a reaction of excited neutral particles, whereas on addition of NH_3 or cyclopropane, the N_3 is formed by a complicated ion-molecule mechanism.

Esters of Carboxylic Acids from Aldehydes and Grignard Compounds

By *Anton Rieker* and *Yasuo Butsugan*[*]

Sterically hindered aromatic Grignard compounds *(1)* react with aldehydes *(2)* to form alcohols *(3)*, and under some conditions also to form ketones *(4)* or esters *(5)*:

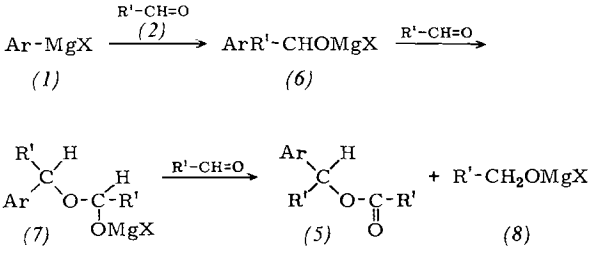


(1) *(2)* *(3)* *(4)* *(5)*

R	R'	*(1)*:*(2)* Mol.-ratio	Yield (%) *(3)*	*(4)*	*(5)*
CH_3	C_6H_5	1:3	trace	27	42
		1:2	17	34	10
$CH(CH_3)_2$	C_6H_5	1:3	—	[a]	52
$C(CH_3)_3$	C_6H_5	1:3	—	—	55
		1:1	60	—	—
$C(CH_3)_3$	CH_3	1:3	24	—	—
$C(CH_3)_3$	H	1:3	5 [b]	—	29 [b]

[a] Detected, but not isolated.
[b] Total yield of *(3)* + *(5)* before separation: 71%.

In every case, *(1)* and *(2)* first give the magnesium compound *(6)* of the alcohol *(3)*. If "oxidizing" aldehydes ($R'=H, C_6H_5$) are used in excess, *(6)* is either dehydrogenated by the aldehyde in a sort of Oppenauer reaction to form the ketone *(4)*, or first adds on the aldehyde to form *(7)*, which is then oxidized to *(5)*. This is accompanied by the simultaneous formation of *(8)*:



(1) *(6)* *(7)* *(5)* *(8)*

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The highest yields of *(5)* are thus obtained when the oxidizing aldehyde *(2)*, $R'=H, C_6H_5$, is present in a 3 M excess. The alcohol to be expected from hydrolysis of *(8)* is found for $R'=C_6H_5$. With "nonoxidizing" acetaldehyde *(2)*, $R'=CH_3$, no ester formation was detected. The yield of *(5)* increases with increasing bulk of the residue R in *(1)* (for R = H: 0%). It appears that the direct Oppenauer oxidation of *(6)* to *(4)* becomes increasingly difficult in this order for steric reasons, with the result that the addition of *(6)* to *(2)* to form *(7)* with subsequent dehydrogenation to give *(5)* predominates.

Maximum Column Inlet Pressure—An Optimum Parameter for Gas-Chromatographic Separations

By *Lutz Rohrschneider*[*]

After a survey of the rules known at present for the optimization of gas-chromatographic separations, the importance of the column inlet pressure for fast analyses with high separation efficiencies is discussed. Practically all the separations investigated that are not carried out with maximum column pressure can be carried out in a shorter time with the same separation efficiency or in the same time with a higher separation efficiency.

Practical examples are described to show that the maximum resolution in a given time for a given column packing is achieved at the maximum pressure with a column length that depends on the column temperature.

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Mechanism of Solid-State Reactions in Hexahalorhenates

By *K. Rössler* (lecturer) and *J. Otterbach*[*]

The thermal annealing of nuclear recoil halide ions in crystalline hexahalorhenates(IV) can be largely attributed to two processes: a solid state exchange *via* ligand vacancies throughout the crystal[1], and combination processes within the disturbed zone produced by the recoil atom. The latter exhibit considerable field effects. In $K_2[ReCl_6]$ and $K_2[ReBr_6]$, electric fields (3—5 kV/cm) inhibit the annealing of recoil halide, whereas the ligand exchange in the corresponding doped systems is not affected. The inhibition decreases with increasing annealing temperature and, in the case of alternating fields, with the frequency. No further inhibition is found at about 200 cycles in the system $^{38}Cl^-/K_2[ReCl_6]$ and at about 110 cycles in the system $^{82}Br^-/K_2[ReBr_6]$.

The rapid hot reactions occurring during irradiation have been studied in $K_2[ReCl_6]/K_2[ReBr_6]$ mixed crystals of varying compositions. The formation of the ^{38}Cl- and ^{82}Br-labeled products can be explained by mechanisms involving zero (primary retention), first (direct substitution) and second order reactions (multi-step process *via* ligand exchange).

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[1] *R. Bell, K. Rössler, G. Stöcklin,* and *S. R. Upadhyay,* Report Jül-625 RC (1969); J. Inorg. Nucl. Chem. (1971), in press.

Medium-Sized Rings of the Peptide Type

By *Manfred Rothe* (lecturer), *Wolfgang Schindler*, *Rainer Pudill*, *Michael Kostrzewa*, and *Rainer Theysohn*[*]

The formation tendency of medium-sized rings of the peptide type on cyclization of linear active peptide derivatives and on incorporation of aminoacyl residues into amide linkages of lactams and diketopiperazines was reported.

Cyclotripeptides, *e.g.* *c*-Sar-Pro-Pro, can be obtained only in exceptional cases from *N*-alkylamino acid peptides and on incorporation of β-amino acids. The ring closure of tripoline is examined as a function of the solvent; high yields of *c*-$(Pro)_3$ are obtained if a chain conformation with *cis*-peptide linkages is stabilized, *e.g.* in pyridine.

N-(mono-β-alanyl)glycine anhydride, *N*-(mono-β-alanyl)-glycine-sarcosine anhydride, and *N*-(mono-β-alanyl)-glycine-L-proline anhydride form ten-membered cyclic tripeptides on aminoacyl incorporation, with intermediate cyclol formation. Similarly, the cyclic tetrapeptide *c*-Pro-Gly-Pro-Gly is formed from *N*,*N'*-bis-(L-prolyl)glycine anhydride. Unstable cyclotripeptides undergo transannular reactions with formation of bicyclic cyclols, anhydrocyclols, and acylamidines.

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Gas-Chromatographic Determination of Arsenic

By *Harald Rüssel* (lecturer) and *Georg Schwedt*[*]

The investigation of some organic arsenic derivatives for quantitative formation, vaporizability, and determinability with the flame ionization detector showed that triphenylarsane is particularly suitable for the gas-chromatographic determination of arsenic. A fast method was developed for forensic purposes. The organ material is dried and burnt in a Schöniger flask. The arsenic in hydrochloric acid solution is extracted as the dithiocarbamate, which is treated with diphenylmagnesium to obtain triphenylarsane and determined by gas chromatography. As little as 1 μg of As/g can be determined in 100 mg of organ; the operation takes $1\frac{1}{2}$—2 hours. Other metals that can be extracted as dithiocarbamates are partly also converted into phenyl compounds, but these are separated gas-chromatographically.

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Potassium Intercalation Compounds in Carbon Fibers

By *W. Ruland*[*]

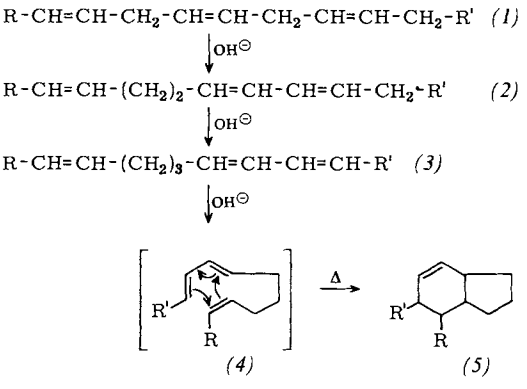
The incorporation of potassium into carbon fibers is investigated by thermogravimetric, electric, and mechanical measurements and by X-ray diffraction (small-angle and large-angle scattering). It is found that despite the absence of discrete absorption stages below the saturation value, defined intercalation compounds of the first stage (insertion between every pair of carbon layers, C_8K) and of the second stage (insertion between every second pair of carbon layers, $C_{16}K$ to $C_{24}K$) are formed. The preferred orientation and the pore structure of the fibers are not affected by the incorporation; the color, as in the case of graphite intercalation compounds, is bronze-brown for the first stage and steel blue to black-blue for the second stage. The X-ray studies show that the potassium layers both in the first and in the second stage are hexagonally close-packed. The transition from the composition $C_{16}K$ to $C_{24}K$ in the second stage is the result of an increase in the concentration of randomly distributed vacancies in the two-dimensional potassium lattice with progressive desorption.

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Synthesis of Indanyl Derivatives from Linear Unsaturated Compounds

By *A. N. Sagredos* (lecturer), *J. D. von Mikusch-Buchberg*, and *Viktor Wolf*[*]

On cyclization of 9,12,15-octadecatrienoic acid *(1a, 1b)* with alkali, the formation of bicyclic carboxylic acids having an indan structure was observed. The following reaction course was proposed:



(a), R = C_2H_5, R' = $(CH_2)_6$-COOH
(b), R = $(CH_2)_7$-COOH, R' = CH_3
(c), R, R' = H, Alkyl

The correctness of this course has been confirmed by synthesis of the postulated intermediates *(2a)* and *(3a)* and their conversion into the indan *(5a)*.

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Directionally Solidified Alloys for High-Temperature Applications

By *P. R. Sahm*[*]

Directional solidification represents a method in which the heat flow at the growth front is regulated by the solidification rate and the temperature gradient. This method has proved valuable in the production of high-

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temperature alloys, particularly what concerns eutectic and the conventional superalloys based on cobalt and nickel, since it brings a remarkable improvement of the mechanical properties. The improvement of properties is mainly due to the unilateral alignment or the complete absence of grain boundaries. Grain boundaries are normally starting points for crack formation, preferred loci for plastic deformation, and areas of increased diffusion. Their absence thus increases the time-dependent creep and the fatigue strength as well as the corrosion resistance. The incorporation of directionally oriented highly elastic phases in one-dimensional, two-dimensional, and three-dimensional forms will, in addition, considerably favor the mechanical properties (yield point and tensile strength) in certain directions. They will be useful wherever anisotropic stress applications are required. Alloys of this type obtained by directional solidification are therefore likely to become the next generation of superalloys.

Adsorbed Layers on Platinum Electrocatalysts

By *Horst Binder, Alfons Köhling,* and *Gerd Sandstede* (lecturer)[*]

Even below their reduction potential and above their oxidation potential, substances are stable in various electrolytes if they are present as monoatomic surface layers. We have investigated the adsorption of elements of the sixth main group on platinum electrodes by the non steady state voltammetric method. Smooth platinum (platinum gauze) and porous platinum (Raney platinum) behave in fundamentally the same way. We have also measured the influence of partial monatomic layers of adsorbed elements on the chemisorption of carbon monoxide, carbon dioxide, formic acid, formaldehyde, and methanol. Potentiodynamic current-voltage curves show that the chemisorption strength of the carbonaceous products changes only when the major part of the platinum surface is covered with the adsorbed element. The adsorbed elements accelerate the anodic oxidation of some substances and retard that of others.

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The Influence of Dispersion on the Coloristic Properties and Fastness Properties of Molybdate Red Pigments

By *Hugo Schäfer*[*]

The color shift of molybdate red pigments toward yellower hues with increasing dispersion time increases with increasing particle size of the pigment under identical external conditions. On the basis of colorimetric investigations, thin-layer electron micrographs, and X-ray diffraction diagrams, it is shown that this color shift is mainly due, not to a simple decrease in the size of the crystals, but to a change in the crystal modification.

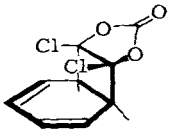
The stabilization-dependent fastness properties, such as light fastness and SO_2 resistance, decrease in molybdate red pigments with increasing dispersion time. This decrease in fastness is partly due to mechanical damage to the stabilizing oxide layer on the pigment grain. Moreover, free, unstabilized fracture surfaces are produced as a result of splitting of the crystals, particularly in the case of large-particle pigments. The observed loss of fastness is therefore greater for large-particle than for small-particle pigments under the same conditions.

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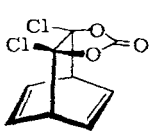
Photosensitized Cycloaddition of Dichlorovinylene Carbonate to Benzene

By *Hans-Dieter Scharf* (lecturer) and *Reinhard Klar*[*]

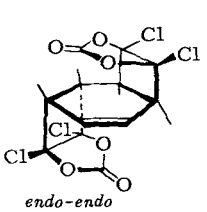
The photochemical cycloaddition of dichlorovinylene carbonate (DCVC) to benzene with acetophenone or acetone as a sensitizer leads to the 1:1 cycloadducts *(1)* and *(2)* and the three stereoisomeric 2:1 cycloadducts *(3a)—(3c)*.



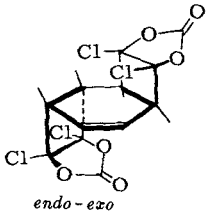
(1) m.p. 147 °C



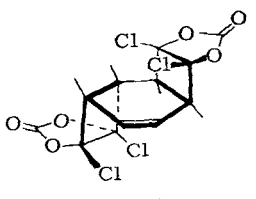
(2) m.p. 194 °C



endo-endo
(3a) m.p. 231 °C



endo-exo
(3b) m.p. 200 °C



exo-exo
(3c) m.p. 244 °C

The structures of these compounds have been verified, and their formation pathways have been investigated. The reaction is based on a triplet mechanism.

The initially formed cycloadduct *(1)* reacts further in the following ways:

1. photosensitized rearrangement into *(2)*, 2. retrocleavage into benzene and DCVC, 3. dimerization to form 2:2 cycloadducts, and 4. formation of the 2:1 cycloadducts *(3b)* and *(3c)* by addition of a further molecule of DCVC.

The existence of *(3a)*, exclusively formed in the reaction mixture of benzene and DCVC, indicates the intermediate occurrence of the *endo*-isomer of *(1)*, which, however, cannot be isolated. An alternative formation path for *(3a)* *via* a charge-transfer complex can be excluded.

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Use of Gel Permeation Chromatography in the Analysis of Fats

By *Harry Scharmann* (lecturer) and *Manfred Unbehend*[*]

Gel permeation chromatography is a suitable method for the assessment of chemical changes in plant and

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animal fats as a result of thermal oxidation during deep-fat frying.

A series of examples are described to show that in addition to partial breakdown of the triglycerides, linkage of the triglycerides to form dimeric and higher molecular weight compounds also occurs. The formation of dimeric triglycerides is confirmed by gas-chromatographic and mass-spectrometric investigations on fractions isolated from a used frying fat by preparative gel permeation chromatography.

Additional information about the formation of oxidized triglycerides is obtained by liquid chromatography on analytical silica gel columns using the Pye liquid chromatography detector.

Investigation of the Reactions of CN-Radicals by Kinetic Spectroscopy

By *M. F. Kamat, D. Perner,* and *R. N. Schindler* (lecturer)[*]

CN-radicals were produced by pulsing gaseous samples of CH_3CN, CCl_3CN, BrCN and $(CN)_2$ respectively in the presence of up to 6 atm argon with 16 nsec pulses of fast electrons. CN formation is attributed to energy transfer from the pressure gas argon to the substrate molecules. In BrCN also the electron capture process contributes to CN-production:

$$BrCN + e^{\ominus} \rightarrow CN + Br^{\ominus}$$

From the rate of decay of the CN-absorption in the presence of additives, absolute rate constants were obtained for the abstraction from molecules like H_2, CH_4, C_2H_6, C_3H_8, $COCl_2$, CCl_4, H_2S, COS, O_2, *etc.* Besides the disappearance of CN, the formation of new absorptions was observed in a number of systems; *e.g.* with O_2 present, the radical NCO was detected; NCS absorption arises in systems containing COS and/or CS_2.

Rate constants were given and the mechanism of the processes was discussed.

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Shift Reagents Without Heavy Metals for NMR Spectroscopy

By *G. P. Schiemenz*[*]

The use of lanthanide complexes as NMR shift reagents is limited to relatively few classes of compounds and solvents. For example, they cannot be used to resolve overlapping signals of phosphonium salts. If the onium center is chosen as the coordination site instead of an electron pair, and an aromatic ring current for the signal shift instead of the metal, one arrives at a valuable alternative which supplements the earlier method. Phosphonium ions form short-lived contact ion pairs, *e.g.* in methylene chloride, with aromatic anions. The center of negative charge is situated close to the phosphorus; α protons, and to a smaller extent β and γ protons, of the cation are sited over an aryl group of the anion, and their signals are displaced to higher fields. For α protons, the effect of the tetraphenylborate anion is usually greater than 1 ppm, and up to about 3 ppm in favorable cases, whereas the effect for β and γ protons is about 20% of the α value. The tris(2,2'-biphenylylene)phosphate ion is even more effective. For example, the signals of the methine protons in the benzhydryltriphenylphosphonium and fluorenyltriphenylphosphonium ions are completely separated from the aromatic signal. The ring current effect differs from the usual anion effect in (a) the magnitude, (b) the direction of the signal shift for β and γ protons, (c) the relative influence on methyl and benzyl protons, (d) the influence on the anisochrony of diastereotopic methylene protons in chiral cations, and (e) the influence on the rotational barrier of phosphonium-substituted dimethylbenzamides. The tetraphenylborates need not be prepared as such, but may be produced by the technique of exchange experiments in the measuring tubes. Salt mixtures give complete averaging, so that the signals can be placed at any desired position between the extreme values. The method can be applied to compounds with acidic functional groups.

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Microbiological Problems of the Preservation of Foodstuffs

By *W. Schmidt-Lorenz*[*]

Like all biosynthetically formed organic material, the foods required for human nourishment are broken down and ultimately mineralized by the microorganisms that occur everywhere in nature. It is becoming increasingly important to improve the keeping qualities not only of the basic foodstuffs but also of the industrially prepared, ready-to-eat meals, which are much more susceptible to attack by microorganisms. The most important requirement is the greatest possible certainty that the foodstuffs are free from food-poisoning and pathogenic microorganisms.

There are fundamentally two methods of eliminating microorganisms and preventing microbial decay:

1. The partial or complete destruction or inactivation of the microorganisms in the food (pasteurization or sterilization) by physical methods, particularly heating or treatment with gases, and more recently treatment with ionizing radiation or chemical preservatives, or the mechanical removal of microorganisms from the substrate (by filtration).

2. Technological modification of the foodstuffs such that the conditions required for the growth of the microorganisms are no longer satisfied (drying, salting, acidification, candying, curing, cooling, and deep freezing).

The general requirements for maximum retention of food value and minimum modification of the food with simultaneous improvement of keeping qualities can probably be achieved only by production and processing of the raw materials under conditions that are as nearly sterile as possible and by a carefully selected combination of preservation means in accurately measured proportions. However, this will depend on a much better knowledge of the microorganisms that occur in the various foods and of their properties.

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The C—H Acidity of Organic Nitriles

By *Wolffram Schröer* (lecturer) and *Ernst Lippert*[*]

With the interaction of the strong base hexamethylphosphoric triamide (HMPT) with a nitrile, *e.g.* acrylonitrile, in an inert solvent (CCl_4, cyclohexane) as an example, high-resolution nuclear magnetic resonance is used to examine the extent to which the complexes formed already have the structure postulated for the transition state of nucleophilic reactions. The proton and ^{13}C shifts and the coupling constants are obtained with LAOCOON III from the ABC or ABCX spectra and used for the calculation of the association constants and of the association energy.

An association constant of $K_x = 4.4$ and an association enthalpy of $\Delta H = -0.63$ kcal/mole are obtained for the association of the base with the α proton at 18 °C in CCl_4, while the values for the β-*trans* proton are $K_x = 9.1$ and $\Delta H = -1.1$ kcal/mole. The proton shifts are 1.013 and 0.305 ppm respectively toward lower fields, and the ^{13}C shifts are 0.49 and 2.99 ppm respectively toward lower fields. The experimental values are explained with the aid of results from CNDO calculations, taking into account the magnetic and electronic anisotropy.

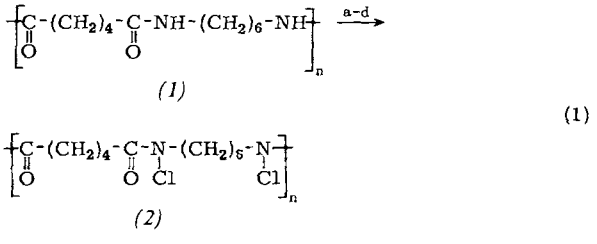
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Syntheses and Reactions of *N*-Chloropolyamides

By *Herman Schuttenberg* (lecturer) and *Rolf C. Schulz*[*]

Nylon 66, nylon 6, nylon 3, poly-*N*-benzylacrylamide, and other polyamides were chlorinated by various methods. The chlorinating agents used were (a) *tert*-butyl hypochlorite, (b) aqueous potassium hypochlorite solution, (c) chlorine dissolved in chloroform, and (d) chlorine oxide.

In accordance with equation *(1)*, for example, nylon 66 *(1)* gives *N*-chloro-nylon *(2)* with 70—100% of the calculated chlorine content (determined iodometrically).



(1) *(2)* (1)

Molecular weight determinations showed that only slight chain degradation occurs with *tert*-butyl hypochlorite. *(2)* is soluble in benzene, chloroform, or dioxane; the IR spectra lack the NH bands at 3300 and 3080 and the amide band at 1530 cm^{-1}.

(2) dissolved in benzene in the presence of pyridine oxidizes secondary alcohols to ketones at 35 °C (molar ratio of *(2)* : alcohol : pyridine = 1.1 : 1 : 1). The yields after 24 hours are 82—95% (determined by gas chromatography), and are higher in some cases than in comparison experiments with *N*-bromohydantoin and *N*-bromoacetamide. The oxidizing capacity decreases on heating or on UV irradiation of *(2)* (in solution or as a film), and the NH and amide bands reappear in the IR spectrum.

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Use of Polymers as Packing Material in Gas Chromatography

By *Hans Schnecko*[*]

The use of three types of polymers for the preparation of efficient separating columns for gas chromatography was described.

1. Liquid ethylene-propylene copolymers can be used as the stationary phase on solid support materials. The separating efficiency for hydrocarbons, aromatic compounds, and other apolar substances is good. The columns are characterized by a remarkable thermal stability, and can be temperature-programmed up to 350 °C.

2. Liquid polyenes with functional end groups (*e.g.* bifunctional polybutadienes and polyisoprenes containing OH, SH, COOH, or Br) form excellent stationary phases for numerous classes of polar and apolar substances; the liquids can be fixed on the support, so that no bleeding from the column is possible.

3. Elastic and thermoplastic foams can be used as column packings in gas-solid chromatography. The products are best prepared by pregrinding. These columns are particularly suitable for the separation of polar components, which then exhibit little or no tailing. The glass transition points of the materials can be determined by *Guillet's* method, and the results agree with those obtained by other methods.

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Measurement of Electron Capture Cross Sections

By *K. G. Mothes, E. Schultes* (lecturer), and *R. N. Schindler*[*]

The secondary electrons formed in an irradiated medium dissipate their excess energy in ionization and excitation processes. When their kinetic energy finally falls below the lowest excitation potential of the molecules surrounding them, the electrons are thermalized and disappear in reactions with electron scavengers and/or in neutralization processes.

Absolute rate constants for the capture of thermal electrons by suitable scavengers can be determined by electron cyclotron resonance. This new method is based on the measurement of the ECR signal in a rapidly flowing gas. It is shown that the integral over the absorption signal $\chi''(H)$ is a direct measure of the number of free electrons per unit volume. Effective cross sections can be determined from the change in the signal magnitude on addition of a scavenger.

The method was described and the influence of the experimental parameters discussed. Measurements on the best-known electron scavengers were reported.

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Determination of the Wetting Behavior of Pigments

By *P.-J. Sell*[*]

In a number of industrial processes, it is very important to know the wetting behavior of powders and pigments. Methods of measurement have been described in which quantities connected with the surface energy (*e.g.* surface or interfacial tensions, contact angles) can be determined on planar surfaces, fibers, and acicular single crystals or on powders and pigments. An example is given to show that the results obtained by the three measurement methods agree. Heats of wetting can be determined from the temperature dependence of the adhesion tension.

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Polarographic and Coulometric Reduction of Actinide(IV)Chlorides in Dimethyl Sulfoxide

By *Ludwig Astheimer* and *Klaus Schwochau* (lecturer)[*]

In order to determine the reduction behavior of the actinides in nonaqueous solvents and to detect their lower oxidation states the chlorides of tetravalent Th, Pa, U and Np were investigated in dimethyl sulfoxide by means of DC and AC polarography as well as potential-controlled coulometry. Two reduction waves were observed for $NpCl_4$ and UCl_4. According to coulometric analysis the first wave with $E_{1/2} = -0.47$ V and $E_{1/2} = -1.22$ V respectively (*vs.* S.C.E.) can be assigned to the reduction to the trivalent state, whereas the second wave with $E_{1/2} = -2.19$ V and $E_{1/2} = -2.16$ V respectively should correspond to the reduction to the metal. At $E_{1/2} = -1.49$ V $PaCl_4$ was also reduced to the metal but the desired trivalent state was omitted. $ThCl_4$ showed a diffusion controlled wave at $E_{1/2} = -1.64$ V which apparently leads to Th(II).

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Mechanism of the Self-Adhesion of Macromolecular Films

By *Peter O. Seidler*[*]

The cause of the adhesion of adhesives, lacquers, metallic coatings, *etc.*, is of a complex nature. The adhesion consequently cannot be traced to a simple principle that could be used as a basis for predicting the possibility of obtaining a satisfactory bond in practice. The situation is simpler in the case of the adhesion of macromolecular films having the same composition (self-adhesion). In this case the physics of solids and of liquids, *i.e.* cohesion, microbrownian movement, diffusion, rheology, *etc.*, can be used to find an explanation, and together with the molecular structure they allow certain predictions regarding the conditions for optimum adhesion.

The microbrownian motion of macromolecule segments is of decisive importance to self-adhesion. This mobility is absent in the vitreous state; self-adhesion can occur only when there is adequate microbrownian motion of sufficiently large segments of macromolecules (ideal limiting case: liquid state). Polyethylene and polytetrafluoroethylene, which are not adhesive at room temperature, are therefore adhesives at higher temperatures. It can therefore be stated that when macromolecular substances are heated, they may pass through not only the states of a glass, a plastic mass, a rubber, and a liquid, but also an adhesive state, which differs from that of the liquid.

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Gram-Scale Preparation of Americium

By *J. Cl. Spirlet* (lecturer) and *W. Müller*[*]

The complete reduction of americium oxide by molten lanthanum or ultrapure hydrogen necessitates shifting of the reduction equilibrium by either distillation of the americium metal[1] or formation of an intermetallic compound[2]. The americium can be separated from the condensed phases and purified by distillation or sublimation.

Several grams of ^{241}Am were prepared by lanthanum reduction of purified oxide or thermal dissociation of Pt_5Am. Repeated distillation and condensation of the metal vapor on tantalum yielded americium with 200 ppm O and 100 ppm N, respectively. By condensation on quartz, americium foils were obtained which could be shaped into electrodes. The samples are being used for the investigation of physico-chemical properties, *viz.*, metallography, crystal structure, heat of dissolution, electrochemical behavior in molten salts.

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[1] *W. Z. Wade* and *T. Wolf*, J. Inorg. Nucl. Chem. *29*, 2577 (1967).
[2] *B. Erdmann* and *C. Keller*, Inorg. Nucl. Chem. Letters *7*, 675 (1971).

The Importance of Physico-Chemical Parameters to the Understanding of Drug Action and to the Rational Development of New Drugs

By *J. K. Seydel*[*]

Many theories, some of them successful, on the relation between biological effects and physico-chemical parameters of a drug molecule have been developed during recent years. The first investigations of this kind, which became the starting point for a new type of drug research, were carried out by *Richet* (1893), *Overton* (1897), *Meyer* (1899), and *Traube* (1903). The reason for looking for structure-activity relations and if possible to predict them is to recognize the qualitative and quantitative significance of the chemical, physico-chemical, and biological properties of a chemotherapeutic agent. This can lead to suggestions for the synthesis of new substances and for substances with special pharmacokinetic properties, or it may be possible to find the most effective compound within a homologous series more quickly. Two kinds of conditions necessary for a biological effect can be differentiated:

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1. chemical properties, which initiate a physico-chemical or chemical reaction at the site of action,

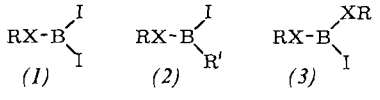
2. physico-chemical properties, which initiate a certain pharmacokinetic behavior, such as absorption, partition, metabolism, and elimination rate in the biological system in question.

An optimum of the parameters of the first condition do not necessarily mean that the parameters of the second condition will also be optimal. However, the parameters that influence the pharmacokinetics frequently have a greater degree of variability. The parameters that are useful for structure-activity relations can be divided into two groups, *i.e.* parameters that predominantly describe the physico-chemical properties and parameters that are more closely related with the chemical reactivity. These parameters may be correlated with the biological data singly or in a multiparameter correlation *(Hansch)*. The correlation of electronic data with the antibacterial effect and of partition coefficients and pK_a values with the binding to serum albumins and the elimination rate is shown in the example of the sulfonamides. The interplay of conditions 1 and 2 for an optimum drug effect is demonstrated.

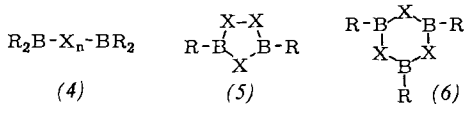
Synthesis and Properties of Selenoboranes

By *Walter Siebert* (lecturer), *Antonio Ospici*, and *Friedrich Riegel*[*]

A comparative study of the stability of the chalcogen-substituted boranes *(1)*—*(6)* (X = S, Se) shows that the selenoboranes rearrange more readily than the corresponding thioboranes. Arylthioboranes having the formulas *(1)* and *(3)* tend only to undergo symmetrization, whereas a 1,2-aryl shift takes place in the selenium compounds,

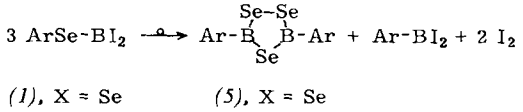


(1) *(2)* *(3)*



(4) *(5)* *(6)*

leading in the case of *(1)* to the formation of triselenadiborolane *(5)*, aryldiiodoborane, and iodine:



(1), X = Se *(5)*, X = Se

The compounds *(1)* and *(2)* with $R = R' = CH_3$; X = S, Se achieve stability by trimerization, a process that fails to occur in *(2)* for steric and electronic reasons when an X atom is inserted into the B—R' bond or when $R' = C_6H_5$ is introduced.

Diboryldisulfanes are relatively stable; *(4)* with $R = CH_3$, $n = 2$ decomposes above 130 °C into *(5)*, BR_3, and S_8. The corresponding selenoborane behaves similarly.

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(1), *(2)*, *(3)* and *(5)* can be prepared by redox reactions between iodoboranes and diselenanes or selenium. The compounds *(4)*, $n = 2$ or $n = 1$ are obtained from R_2BI and Cp_2TiSe_5 or $(R_2SnSe)_3$; the product with $n = 1$ readily forms polymeric *(6)*.

Extraction Chromatography with High-Porosity Polymers

By *Markus Stoeppler* (lecturer), *Ivan Havezov* and *Safa Äl-Murab*[*]

Styrene-divinylbenzene copolymers (SDVB) were examined for use as support materials in extraction chromatography.

The large specific surface area (up to 850 m^2/g) leads to the uptake even of relatively low-boiling solvents, and this leads to a distinct analogy with the processes that occur in liquid extraction. Matrix effects that are frequently observed also affect the capacity.

In kinetic studies, the diffusion within the SDVB grains was found to be the rate-determining step. The HETP values attainable (≤ 0.6 mm) are independent of the flow rate over a wide range.

The versatility of these materials is illustrated by a number of very selective separations for the elements iodine, tellurium, gold, uranium, and neptunium.

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Metabolism of Carcinogenic Purine *N*-Oxides

By *Gerhard Stöhrer* (lecturer) and *George B. Brown*[*]

The chemical carcinogens 3-hydroxyxanthine and guanine 3-oxide are converted *in vivo* into reactive metabolites. Rats treated with 3-hydroxyxanthine excrete 8-chloroxanthine and 8-methylthioxanthine. These metabolites are products of the 8-substitution reaction of 3-acyloxypurines, which can be studied with synthetic 3-acetoxyxanthine. A protein fraction from rat liver catalyzes this reaction by the intermediate formation of sulfates and phosphates of the *N*-hydroxypurines. A noncarcinogenic derivative, 7-methyl-3-hydroxyxanthine, does not react in this way, and does not lead to 8-substituted metabolites.

The reactions of 3-acetoxyxanthine with biological molecules were finally described.

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Unidirectional Solidification of Pseudobinary Eutectics in Ternary Systems with Copper as the Matrix

By *Heinz Sprenger* (lecturer) and *Julius Nickl*[*]

In ternary systems containing copper, eutectics suitable for unidirectional solidification have been found on pseudobinary sections between copper (matrix) and the E phases MCuSi and MCuGe (M = Ti, Zr, Hf). The investigations were carried out with the system Cu/ZrCuSi

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as a model. The samples produced at solidification rates of 1 to 20 mm/min show a fibrous morphology, with the ZrCuSi fibers of 1—5 μm in diameter and 100—500 μm in length lying more or less parallel to one another in the copper matrix.

The degree of alignment and the morphology of the eutectic depends on the temperature gradient and the solidification rate. The crystallographic orientation in the growth direction was found by rotating-crystal photographs to be $[001]_{Cu} \| [001]_{ZrCuSi}$.

A tensile strength of about 40 kg/mm^2 was found on measurement of the mechanical properties. The high electrical conductivity of the eutectic (10—20% lower than that of copper) is due to the low solubility of Zr and Si in the copper matrix.

Information and Documentation in Food Science

By *Berend Strahlmann*[*]

Since the beginning of the 19th century, when *J. H. Becker* listed 7276 titles from the literature known to him in the field of "nutrition science", the number of publications on food science has multiplied every year, particularly since the handbooks and scientific periodicals started to distinguish food science as a new discipline. Abstracting systems that soon appeared found themselves in difficult situations, not only because the food field is also covered by other scientific fields with their own abstracting services, with the result that some of the publications are abstracted twice while others are not abstracted at all, but also because the existing documentation systems can no longer cope with the information explosion. One way out of this dilemma is offered by conversion to electronic data processing and international cooperation, such as has been achieved *e.g.* by the International Food Information Service (IFIS) and with a still wider scope in a neighboring field by the International Nuclear Information System (INIS).

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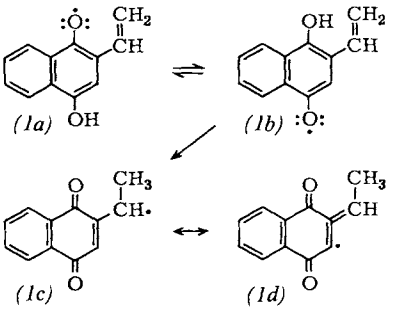
Formation and Properties of 2,3-Bis(1,4-naphthoquinone-2-yl)butanes

By *Winfried Storck* (lecturer) and *Georg Manecke*[*]

No 2-vinylnaphthoquinone is obtained on alkaline hydrolysis of 1,4-diacetoxy-2-vinylnaphthalene and subsequent oxidation in an acidic medium. Instead, three dimerization products derived from the rearranged semiquinone *(1c)* or *(1d)* were found; these products are *meso*- and *rac.*-2,3-bis(1,4-naphthoquinone-2-yl)butane and 6,13-dimethyl-6,13-dihydro-5,14;7,12-pentacenediquinone.

The 2,3-bis(naphthoquinonyl)butanes, which are of interest as models for polymeric redox systems, were therefore prepared independently by Wurtz reaction from 2-(1-haloethyl)- and 2-methyl-3-(1-haloethyl)-1,4-naphthoquinones. All the isomeric dimerization products of the radicals *(1c)* and *(1d)* were isolated.

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The oxidative potentiometric titration of the diastereoisomeric naphthohydroquinonylbutanes showed that the half-wave potentials and the formation constants for the semioxidized intermediates are influenced by the substitution on the quinone nucleus and by the configuration.

[1] *W. Storck* and *G. Manecke*, Chem. Ber. *104*, 1207 (1971).

Attempts to Detect Monomeric Hexadecylketene on Thermal Decomposition of Isopropenyl Stearate

By *H. J. Strauss* (lecturer) and *J. D. von Mikusch-Buchberg*[*]

NH or OH groups that are difficult to acylate are converted into the corresponding *N*- and *O*-acyl compounds by isopropenyl stearate under acid catalysis with elimination of acetone.

The active acylating agent in this reaction is thought to be free hexadecylketene, which is also thought to be formed when isopropenyl stearate is heated alone in inert hydrocarbons.

IR spectroscopic studies on such thermolysis products and their reactions with *tert*-butanol and cyclopentadiene gave no indication of free monomeric ketene. A tetrameric hexadecylketene is formed as a stable reaction product.

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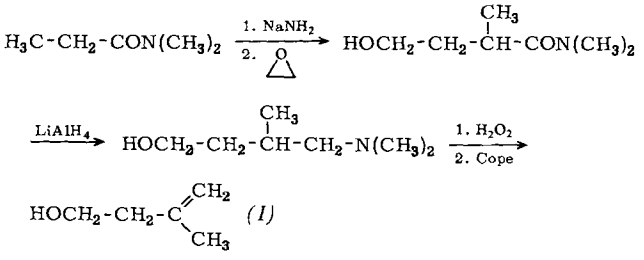
Hydroxyalkylation of Dialkylamides of Carboxylic Acids with Epoxides

By *Wolfgang Sucrow* (lecturer), *Marion Slopianka*, and *Dieter Winkler*[*]

N,N-Dialkylcarboxamides (*e.g.* dimethylacetamide, dimethylpropionamide, dimethylphenylacetamide, or *N*-methylpyrrolidone) are deprotonated with sodamide in liquid ammonia to form the α-carbanions, which can be alkylated with epoxides (*e.g.* ethylene oxide, 1,2-butylene oxide, isobutylene oxide, or styrene oxide) in moderate to satisfactory yields to obtain the amides of γ-hydroxy acids. *trans*-2,3-Butylene oxide does not react, whereas the *cis* form reacts with dimethylacetamide to form a small quantity of 2-methyl-3-hydroxyvaleric dimethylamide. The formation of by-products (lactones and glycol ethers) is discussed.

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Some of the dialkylamides of γ-hydroxy acids are reduced by $LiAlH_4$ to the amines, which give 3-buten-1-ols on oxidation with hydrogen peroxide and Cope degradation. The naturally occurring isopentenol *(1)* is obtained in this way from ethylene oxide and dimethylpropionamide:



(1)

Temperature Dependence of the Hydrolysis of Esters by Trypsin and Chymotrypsin

By *Gerhard Talsky* (lecturer) and *Christian Gramsch*[*]

The investigation of the temperature dependence of the hydrolysis of esters, amides, and proteins by trypsin and chymotrypsin in small temperature intervals has shown that these enzyme-substrate systems do not give a continuous straight line when log v_{br} is plotted against $1/T$. It is necessary to distinguish between linear regions and wave-like regions. This behavior can be explained by changed reaction conditions resulting from small temperature-induced changes in the conformation of the enzyme.

Effects of the pH value, of salts and urea, and of thermal denaturation indicate only an *indirect* connection between the activity and the anomalies.

The separate investigation of the overall reaction, the acylation step, and the deacylation step in the hydrolysis of cinnamoylimidazole by trypsin led to the conclusion that the elementary step in which the anomalies occur takes place before the formation of the acylenzyme. If one also considers the experiments with inhibitors, the reason for the anomalies seems to lie in the modified bonding of the substrate.

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New Determination of the ^{238}U(sp.f.)Decay Constant *via* Fission Tracks in an Antique U-Stained Glass of Known Age

By *Klaus Thiel* (lecturer) and *Wilfrid Herr*[*]

A new determination of the decay constant for the spontaneous fission of ^{238}U was carried out by means of an artificial U-glass from the middle of the last century with engraved dedication and carrying the date "1844".

The beaker was very probably made in the same year. From the number of spontaneous fission tracks recorded until now and the fission tracks induced by irradiation with an accurately known dose of thermal neutrons, it was calculated that the fission constant of ^{238}U is $\lambda_{sp.f.} = (8.57 \pm 0.42) \times 10^{-17} a^{-1}$. The neutron dose was measured by the gold foil technique, the absolute value of the ^{198}Au activity being determined by β-γ coincidences.

By counting sufficiently large areas, it was possible to reduce the simple statistical error of the spontaneous fission tracks to less than 1.66%, and that of the induced fission tracks to less than 0.35%.

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Gas-Chromatographic Determination of Residues from Pesticides (Carbamates, Ureas, Amides) in Plant Material

By *Hans-Peter Thier*[*]

The residue analysis of herbicidal ureas and amides and of carbamates used as insecticides or germination inhibitors was described. The plant material is treated in the same way as for the determination of chlorinated hydrocarbons and organophosphates. Thus the diluted acetonitrile extract is extracted with petroleum ether and dichloromethane (8:2), and the organic phase is purified by passage through a Florisil column. The purified extracts are first examined for chlorinated hydrocarbons and organophosphates by gas chromatography, and are then treated with a mixture of bromine (5% iodine) and water or with a solution of bromine (5% iodine) in glacial acetic acid. This leads to the formation of bromine derivatives of the carbamates, ureas, and amides, which are then determined gas-chromatographically with the electron capture detector under the same conditions as in the determination of chlorinated hydrocarbons and organophosphates.

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Electron Spectroscopic Studies of Adsorbents and Catalysts

By *J. M. Thomas*[*]

After briefly outlining the essence of electron spectroscopy and its potential impact in the study of solid surfaces, two typical examples were discussed. First, the study of compositional changes (variations in surface stoichiometry) in alloys following exposure to gas; and, second, the presence of adsorbed, or intercalated, atoms in graphitic carbon.

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Mechanism of Formation of Polywolframates and -molybdates in Aqueous Solution

By *Karl-Heinz Tytko*[*]

The elongation of the M—O bond resulting on protonation of the MO_4^{2-} ion (M = W, Mo) creates a situation in which the tetrahedral coordination sphere of the M atom can be expanded into an octahedral one by simple *addition* involving an overall gain in energy. In this a non-protonated MO_4^{2-} ion, a further HMO_4^- ion (or if present

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a H_2MO_4 molecule), or an addition product already formed and having MO_6 octahedra can act as bidentate ligand. As confirmed by experimental results, such a simple addition reaction can proceed very rapidly. Of the many possible aggregates that can be formed according to this principle, those ring-shaped aggregates built up exclusively of octahedra which result from participation of an *intra*molecular addition step command particular attention: Their structures are the kinetically most stable that can be formed by this addition principle since removal of a WO_4 unit entails simultaneous destruction of at least two octahedra. For statistical reasons and in agreement with experimental results only four-membered "rings" as the smallest possible rings are to be expected.

Consideration of the acid/base properties of the aggregates affords additional information about the mechanism of aggregation. The basicity of the base function of the HMO_4^- ions in the aggregate depends upon the number of terminal O atoms present in the octahedron made up of HMO_4^- ion. (The H atom of the HMO_4^- ion, however, does not correspond to an acid function.) Aggregation therefore proceeds in such a manner that formation of the energetically favorable base function MO_n^- having large n is promoted. One particular consequence is that the H atoms occupy predominantly bridging O positions. Also to be considered is that, in the pH range in which significant aggregation takes place ($pH < 8$), the base functions MO^- (octahedra with one terminal O atom) and $M—O^- \cdots M$ (octahedra having no terminal O atom) can only exist in the protonated form. This additional protonation for octahedra having just one terminal O atom or none at all is the main regulatory principle in the aggregation process when there is a lack of H^+ ions (initial ratio $H^+/MO_4^{2-} \lessapprox 1$): On the one hand these H^+ ions could be used for protonation of additional MO_4^{2-} ions and the HMO_4^- ions for the building of more octahedra (energy gain); on the other hand the higher protonation of the polyanion reduces the electrostatic repulsion energy between the negative charges.

If the partitioning of a structure and of the related reaction pathway is carried out far enough, the free energy of reaction ΔG_r for the case in question can be visualized as being made up of increments for the different units. Thus ΔG_r is given by the sum over the products of frequency and ΔG_r increment of the structural units. Because of the scarcity of H^+ ions in the acidification range $\lessapprox 1$, a comparison of the many different structures that are possible according to the addition principle requires a standardization of the frequency of the structural units with reference to the use of a given number of H^+ ions. It then becomes apparent that, in terms of the limiting values for *relative* values of the ΔG_r increments estimated within adequate safety factors, the planar four-membered "ring" is not only the kinetically most stable but also by far the energetically most favorable polymetalate species according to the addition principle.

Similar arguments regarding the subsequent course of aggregation lead, in the case of a scarcity of H^+ ions, to a hexawolframate ion $[W_6O_{19}(OH)_3]^{5-}$ (parawolframate A) formed by 7 H^+ and 6 WO_4^{2-} for the H^+/WO_4^{2-} system, which is in agreement with experimental findings, and to a heptamolybdate ion $Mo_7O_{24}^{6-}$ formed by 8 H^+ and 7 MoO_4^{2-} for the H^+/MoO_4^{2-} system, also in accord with experiment, as the thermodynamically most stable species formed by a *condensation* mechanism. The difference between the two systems arises from the reduced tendency of the $HMoO_4^-$ ion to undergo aggregation and the resulting participation of H_2MoO_4 in the aggregation.

High Pressure Column Liquid Chromatography with Modified Porous Silica as Stationary Phase Material

By *Klaus Unger* (lecturer) and *Peter Ringe*[*]

High pressure column liquid chromatography has been developed in recent years as a new chromatographic method. High separation efficiencies are not only influenced by the elution rate, the nature of the mobile phase, and the column dimensions but also by the properties of the porous particles used as stationary phase. These properties include the shape and the diameter of the particles, the parameters of the pore structure, and the chemical composition of the surface.

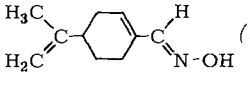
Porous silica is particularly suitable as stationary phase material for high pressure column liquid chromatography. It can be produced in the form of spherical particles and in form of porous layers on nonporous particles. Its pore structure and the polarity of its surface can be varied within wide limits. The influence of these properties on the chromatographic separation was investigated and discussed for examples from adsorption, partition, and gel permeation chromatography.

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Synthetic Sweeteners from Oximes

By *Bernard Unterhalt* (lecturer) and *Lothar Böschemeyer*[*]

Isomeric oximes can have different physiological effects. For example, according to our experience, (*E*)-*p*-methoxybenzaldehyde oxime and (*E*)-*p*-methylbenzaldehyde oxime taste sweet, while the (*Z*) isomers do not. Contrary to earlier reports, perillaldehyde oxime *(1)*, as an α-alkyl-α,β-unsaturated oxime, for steric reasons occurs only in the (*E*) form, which has a sweetening factor of 1400—2000. This behavior was confirmed for the basic structure by the investigation of 1-cyclopentenecarbaldehyde oxime and 1-cyclohexenecarbaldehyde oxime.



(1)

The reduction of oximes leads *inter alia* to amines, which react with chlorosulfonic acid to form the salts of the corresponding sulfamic acids. These were tested for their sweetening properties in analogy with cyclamate. The investigations led to a series of alkylsulfamates and cycloalkylsulfamates having sweetening properties comparable with those of cyclamate; toxicity tests are currently being carried out on these products.

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The Use of Silylation Reactions in Foodstuff Analysis

By *Werner Untze*[*]

The introduction of the trimethylsilyl group into compounds having replaceable hydrogen atoms has become important both in preparative and in analytical chemistry[1].

Silylation products are characterized by greater ease of volatilization and by a greater stability in the vapor phase. Thus phenolic compounds (*e. g.* antioxidants, preservatives), amino acids, carboxylic acids, steroids, and some carbohydrates can be silylated with suitable silylating agents (*e. g.* *N,O*-bis(trimethylsilyl)trifluoroacetamide, hexamethyldisilazane, trimethylchlorosilane, *N*-trimethylsilylimidazole), and can then be separated and determined by gas chromatography[2]. Polyhydroxy compounds containing water may be allowed to react, after partial drying, with *N*-trimethylsilylimidazole or with *N,O*-bis(trimethylsilyl)trifluoroacetamide and determined gas-chromatographically[3]. Free fatty acids and in some cases hydroxy acids have been detected and determined with the aid of a suitable silylation reaction.

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[1] *L. Birkofer* and *A. Ritter* in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie, Vol. 5. Verlag Chemie, Weinheim 1967, p. 185.

[2] *D. L. Stelling et al.*, Biochem. Biophys. Res. Commun. *31*, 616 (1968); *E. D. Smith et al.*, Nature *208*, 878 (1965); *W. Wachs et al.*, Dtsch. Lebensmittel-Rdsch. *66*, 37 (1970).

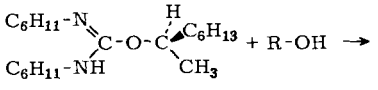
[3] *M. G. Horning et al.*, Biochim. Biophys. Acta *148*, 597 (1967).

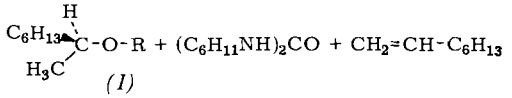
The Mechanism of Alkylation with *O*-Alkyl-*N,N'*-Dicyclohexylisoureas

By *Erich Vowinkel* (lecturer) and *Rolf Jaeger*[*]

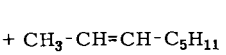
O-(2-Octyl)-*N,N'*-dicyclohexylisourea reacts with acetic acid or phenol in a four-step process. The reaction rate is determined by two successive steps, one of which is bimolecular and the other unimolecular. The bond cleavage precedes the formation of the new bond. The intermediate 2-octyl cation can react to form 1-octene or 2-octene instead of the ester *(1a)* or the ether *(1b)*; its occurrence is verified by the detection of the products resulting from hydride shifts and by interception reactions.

The reaction to form 2-octyl acetate proceeds in cyclohexane or acetonitrile with 100% inversion. This observation, which is surprising for an S_N1 reaction, is explained by ion-pair participation.





(1)



(a), R = CH_3CO; *(b)*, R = C_6H_5

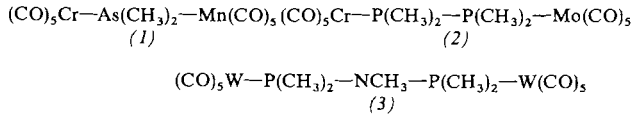
The ether formation is also associated with inversion; the stereospecificity is 99.3%. The ring alkylation that occurs simultaneously in a side reaction also proceeds stereospecifically.

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Base-Bridged Dinuclear Carbonylmetal Complexes

By *Heinrich Vahrenkamp* (lecturer) and *Winfried Ehrl*[*]

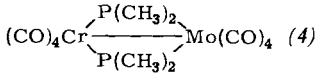
Three kinds of dinuclear transition metal complexes, in which the two metal atoms were bridged by one, two, or three basic atoms, were prepared. Examples of these complexes, in which nitrogen, phosphorus, arsenic, oxygen, and sulfur act as the basic atoms, are *(1)*, *(2)*, and *(3)*:



(1) *(2)*

(3)

The complexes were examined for their ability to act as precursors of more highly aggregated metal-metal linked clusters. On thermolysis and photolysis, however, the types *(1)* and *(3)* undergo disproportionation to form mononuclear complexes. The type *(2)*, on the other hand, loses CO when heated, with formation of compounds such as *(4)*.



(4)

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Application of ^{13}C Resonance to Stereochemical Problems in Carbohydrates

By *Wolfgang Voelter* (lecturer), *Eberhard Breitmaier*, and *Günther Jung*[*]

The CAT method has been used in the past for the routine recording of ^{13}C resonance spectra; this method has the disadvantages of long recording times and high stability requirements with regard to the NMR equipment. By accumulation of pulse spectra and Fourier transformation[1-5] of the interferograms, on the other hand, useful ^{13}C resonance spectra can be recorded in a short time. According to our investigations, it is advantageous, as in proton resonance spectroscopy, to use tetramethylsilane as the standard, since the frequently used carbon disulfide gives a ^{13}C signal that may overlap with that of carbonyl carbon atoms.

A definite signal assignment is possible for many open-chain polyalcohols even without the use of "off-resonance" decoupling[1]. The ^{13}C signals of the CH_3 or CH_2 groups of deoxypolyols occur at highest field, the C atoms of primary alcohol groups are more strongly shielded than

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those of secondary alcohol groups, and "identical" C atoms in symmetrical polyols give signals of stronger intensity. The methylglycosides are particularly suitable for the systematic investigation of the conformation of carbohydrates by means of ^{13}C resonance, since they exhibit no mutarotation[6]. The signals of the glycoside C atoms of the pyranose ring appear at the lowest fields. The resonances of the hydroxymethylene C atoms are most strongly shielded in hexoses. In pentoses the ring methylene C atom signals appear at highest field. C atoms with axial substituents generally give signals at higher fields than comparable C atoms with equatorial substituents. This rule allows the determination of the conformation of a sugar. Thus D-arabinose, unlike most other sugars, has the 1C conformation[7].

[1] *W. Voelter, E. Breitmaier, G. Jung, T. Keller,* and *D. Hiss,* Angew. Chem. *82,* 812 (1970); Angew. Chem. internat. Edit. *9,* 803 (1970).

[2] *G. Jung, E. Breitmaier, W. Voelter, T. Keller,* and *C. Tänzer,* Angew. Chem. *82,* 882 (1970); Angew. Chem. internat. Edit. *9,* 894 (1970).

[3] *H. Günther* and *T. Keller,* Chem. Ber. *103,* 3231 (1970).

[4] *C. Tänzer, R. Price, E. Breitmaier, G. Jung,* and *W. Voelter,* Angew. Chem. *82,* 957 (1970); Angew. Chem. internat. Edit. *9,* 963 (1970).

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[6] *E. Breitmaier, W. Voelter, G. Jung,* and *C. Tänzer,* Chem. Ber. *104,* 1147 (1971).

[7] *W. Voelter, E. Breitmaier, R. Price,* and *G. Jung,* Chimia *25,* 168 (1971).

The Photochemical *cis-trans* Isomerization of *n*-Octenes in the Presence of Organoaluminum Compounds

By *Siegfried Warwel* (lecturer) and *Heinz-Peter Hemmerich*[*]

The *n*-octenes with nonterminal double bonds undergo *cis-trans* isomerization on irradiation with UV light or γ rays even at room temperature whenever molar quantities of an organoaluminum compound ($HAlR_2$ or AlR_3) are present. This configurational isomerization, which does not occur under otherwise identical conditions without irradiation or in the absence of $HAlR_2$ or AlR_3, proceeds without the slightest shift of the C=C double bond in the olefin molecule, and leads with all octenes, irrespective of the configuration, to the thermodynamically stable equilibrium mixture of the *cis-trans* isomers. A distinct dependence of the isomerization on the temperature and on the organoaluminum species is observed, particularly when UV light is used. On replacement of AlR_3 by tetraalkyltin, a pure *cis-trans* isomerization of the monoolefin used is also observed under analogous conditions.

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Sources of Information for the Determination of the Effectiveness of Corrosion Prevention with Thermosets

By *Josef Wagner*[*]

The change in effectiveness with time is of special industrial and economic importance in every field of corrosion prevention. In cases of metallurgical corrosion prevention, the behavior toward a given medium can usually be accurately determined. On the other hand, conclusive information on the effect of a thin protective surface coating, *e. g.* in passive corrosion prevention with thermosets, is much less commonly available, the main reason for this being lack of coordination of practice with analytical test methods. This shortcoming can also be seen from the lack of suitable standards.

In view of the worldwide importance of the protection of industrial installations against corrosion, it is desirable to build up an information system that shows as accurately as possible, and with specific reference to practical conditions, how long effective protection can be expected by a given means against a specified medium, *i. e.* the number of years of maintenance-free protection provided.

Information sources of this type that were mentioned in the lecture are technological punched cards, resistance lists, and simulated practical tests for laboratory use in individual corrosion-prevention cases. The results of testing experience covering a period of ten years are summarized in this work.

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Rapid Radiochemical Separations by Electrolytic Removal

By *Max Weber* (lecturer), *Alfred Stelter,* and *Günter Herrmann*[*]

The release of 3.1 min ^{208}Tl from cathodic layers of its parent substance 60 min ^{212}Bi in aqueous media was investigated. It is shown that release occurs within seconds even for layers several mg/cm^2 thick. The α-recoil of the ^{208}Tl plays an essential part here. On the one hand, it results in the loss of 50% of the ^{208}Tl for the removal, while on the other hand, it overcomes an adsorption of small amounts of thallium that depends on the electrical potential of the cathode. Consequently, the behavior of ^{208}Tl differs considerably from that of thallium that does not originate from recoil processes. Applications of the release technique in the study of shortlived nuclides and also of electrochemical processes are discussed.

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Photophysical Primary Processes

By *Albert Weller*[*]

On absorption of a light quantum, the energy content of the absorbing molecule is increased and its electron density distribution is changed. This leads to characteristic changes in the dipole moment, the acid and base strength, the ability to associate, and the electrochemical potential. The reactions that are possible in the excited state as a result of these changes can be investigated by luminescence and flash spectroscopic methods, and their half-lives can be determined by comparison of the lives of the excited reactants as found by intramolecular (radiative and radiationless) deactivation processes.

Of the bimolecular processes studied,

1. proton transfer (dissociation of acids, hydrolysis of bases, acid-base reactions)

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2. complex formation (excimer and hetero-excimer formation)
3. electron transfer (univalent redox processes)
4. H-atom transfer ("simultaneous" proton and electron transfer),

all of which are reversible, *i.e.* revert rapidly to the original ground state configuration and are not therefore usually regarded as photochemical reactions, 1 and 2 lead to fluorescence transformation (*i.e.* the excited state persists), while the fluorescence is quenched in 3 and 4.

As is shown by the rate constants found, the reactions are all diffusion-controlled, and the actual reaction step that occurs in the encounter complex has frequencies of the order of $10^{11}\ s^{-1}$.

Some Recent Results from the Chemistry of Borazine-Metal Complexes

By *Helmut Werner* (lecturer), *Edith Deckelmann*, and *Karl Deckelmann*[*]

In the search for reactive starting compounds for the synthesis of the complexes $R_3B_3N_3R'_3M(CO)_3$ [M = Cr, Mo, W; R = R' = alkyl], a series of new nitrile complexes of the type *cis*-$(RCN)_3M(CO)_3$ were prepared, and their chemical and physical properties were studied. These investigations led to the first preparation of the hexaalkylborazine-molybdenum complexes $Me_3B_3N_3Et_3Mo(CO)_3$ and $Et_3B_3N_3Me_3Mo(CO)_3$, with a maximum yield of 5%, by three different reaction paths:

1. reaction of *cis*-$(MeCN)_3Mo(CO)_3$ or *cis*-$(PhCN)_3Mo(CO)_3$ with $R_3B_3N_3R'_3$ under rigorously controlled conditions in a high vacuum;
2. the action of $R_3B_3N_3R'_3$ on the addition compound $[(MeCN)_3Mo(CO)_3]_2 \cdot C_4H_8O_2$, which is obtained from *cis*-$(MeCN)_3Mo(CO)_3$ and dioxane, in a high vacuum;
3. photochemical reaction of $Mo(CO)_6$ with $R_3B_3N_3R'_3$ at ≈ 20 torr.

Intermediate compounds having the composition $R_3B_3N_3R'_3Mo(CO)_5$, which are stable in solution at room temperature, are formed.

The hexaalkylborazine-metal complexes $R_3B_3N_3R'_3M(CO)_3$ [M = Cr, Mo] are kinetically labile, and react very rapidly even with weak nucleophiles. The extreme reactivity is closely related to the bonding, which is discussed on the basis of IR, NMR, and X-ray structural investigations.

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The Occurrence of Various Trypsin and Chymotrypsin Inhibitors in Peas

By *Jürgen Weder*[*]

Preliminary investigations showed that eight inhibitors that are active against trypsin and chymotrypsin are present in peas (*Pisum sativum* L.). The inhibitors were extracted from crushed peas with 0.25 N H_2SO_4, concentrated by fractional precipitation with ammonium sulfate (20—80% saturation), and freed from inactive proteins by filtration through a trypsin-resin column. Five electrophoretically homogeneous inhibitors have been isolated from this mixture by preparative polyacrylamide gel electrophoresis (system: glycine/tris pH = 8.3; 6 M in urea, anodic) in two stages (concentration followed by purification).

The specific activities are different. 1 mg of the inhibitors provides 100% inhibition of 0.84—3.1 mg of trypsin and 1.0—2.4 mg of α-chymotrypsin. The amino acid analysis shows the absence of methionine in all the inhibitors, and with one exception, the absence also of cysteine. The molecular weights (averages from the amino acid analysis, specific activity against trypsin and α-chymotrypsin, and polyacrylamide gel electrophoresis by the Na dodecyl sulfate method) are between 10000 and 12000.

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Crosslinking of Polyethylene in the Presence of Additives

By *Rudolf Wiedenmann* (lecturer) and *Helmut Markert*[*]

Peroxides that seem suitable for the crosslinking of polyethylene were decomposed in paraffinic hydrocarbons (models for PE) at 150—180 °C, and the liberation of gas and the composition of the reaction gases were investigated as a function of the peroxide concentration and of the decomposition temperature. In the case of dicumyl peroxide (Di-Cup) and 1,3-bis(*tert*-butylperoxyisopropyl)benzene (m-P14), the other decomposition products were also determined, and the rate constants, half-lives, and activation energies were determined by measurement of the gas volumes instead of by the usual back-determination of the peroxide concentration.

With Di-Cup and m-P14, methane is the only gaseous reaction product formed, apart from traces of other gases. The reaction gas in the case of m-P14 also contains the volatile cleavage products acetone and *tert*-butanol. The formation of methane can be considerably reduced if additives such as selected polymethines or special aromatic compounds are introduced to intercept the methane-forming methyl radicals that are formed as secondary cleavage products of the peroxide as a function of the crosslinking temperature. The influence of these additives on the decomposition mechanism of the peroxides and on the degree of crosslinking of crosslinked films was investigated.

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Erythrocuprein

By *Ulrich Weser*[*]

Erythrocuprein, a greenish-blue Cu protein with a molecular weight of 32 600, was isolated from bovine erythrocytes. It was prepared using chloroform-ethanol extraction extended by DEAE chromatography and additional gel filtration steps[1]. As in the case of erythrocuprein from human erythrocytes[2], two additional atoms of Zn per molecule were detected here. Thus, bovine erythrocuprein can also be considered to be a Cu—Zn protein[1, 3]. Spectroscopic studies at 77 °K show a fivefold increase in the inten-

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sity of the Cu absorption band at 670 nm and the shoulder at 430 nm is more distinct. It can be concluded from ESR measurements that Cu^{2+} is bonded to several nitrogen atoms[1,4]. On titration of erythrocuprein with dithionite under argon, the metalloprotein takes up two electrons, *i.e.* one electron per Cu^{2+}. CD and MCD measurements indicate a small helical portion in the protein residue. After incubation of erythrocuprein in 1% sodium dodecyl sulfate and 4M urea, monomeric and tetrameric units, which can be separated by electrophoresis, are formed. The erythrocuprein obtained by the usual preparative methods is dimeric. Apart from a dismutase reaction[5], *i.e.* the disproportionation

$$O_2^{-\bullet} + O_2^{-\bullet} + 2H^+ \rightleftharpoons O_2 + H_2O_2$$

no biochemical reaction of this metalloprotein could be detected.

[1] *U. Weser, E. Bunnenberg, R. Cammack, C. Djerassi, L. Flohé, G. Thomas,* and *W. Voelter,* Biochim. Biophys. Acta *243*, 203 (1971).

[2] *R. C. Carrico* and *H. F. Deutsch,* J. Biol. Chem. *245*, 723 (1970).

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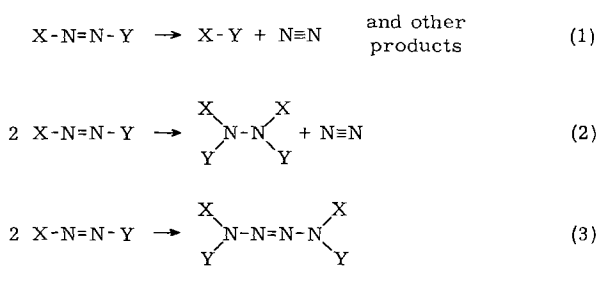
[4] *G. Rotilio, A. F. Agrò, L. Calabrese, F. Bossa, P. Guerrieri,* and *B. Mondovi,* Biochemistry *10*, 616 (1971).

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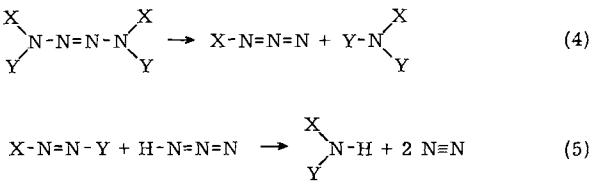
Thermal Decomposition of Azosilanes

By *Nils Wiberg* (lecturer) and *Wilfried Uhlenbrock*[*]

The thermolysis of azo compounds X—N=N—Y can proceed with decomposition [eq. (1)], disproportionation [eq. (2)], and, as we have also found, dimerization [eq. (3)]:



Whereas azoalkanes (X, Y = H, alkyl) undergo "decomposition" and "disproportionation"[1,2], the azosilanes (X, Y = H, silyl) undergo "disproportionation" and "dimerization". The products of the thermolysis of $Me_3Si—N=N—SiMe_3$ or reaction of $Me_3Si—N=N—SiMe_3$ with $Me_3Si—N=N—H$ are accordingly $(Me_3Si)_2N—N(SiMe_3)_2$ or $(Me_3Si)_2N—NH(SiMe_3)$ (free radical formation) and $(Me_3Si)_2N—N=N—N(SiMe_3)_2$ or $(Me_3Si)NH—N=N—NH(SiMe_3)$ (non-radical formation)[3]. Since silylated tetrazenes, as we have found, can decompose in accordance with eq. (4) and hydrazoic acid reacts with azosilanes in accordance with eq. (5), azides, amines, and nitrogen are found under "special" reaction conditions as the end products of a dimerization reaction.



Thus a mixture of $Me_3Si—N=N—SiMe_3$ and LiMe (intermediate formation of $Me_3Si—N=N—Li$) gives LiN_3 and $LiN(SiMe_3)_2$ in a molar ratio of 1:1, while a mixture of $Me_3Si—N=N—SiMe_3$ and hydrochloric acid (intermediate formation of H—N=N—H) gives, *inter alia*, NH_3 and nitrogen in a molar ratio of 1:1.

[1] *Houben-Weyl-Müller:* Methoden der organischen Chemie, Vol. 10/2. Thieme-Verlag, Stuttgart 1967, p. 790.

[2] *T. Tsuji* and *E. M. Kosower,* J. Amer. Chem. Soc. *93*, 1992 (1971).

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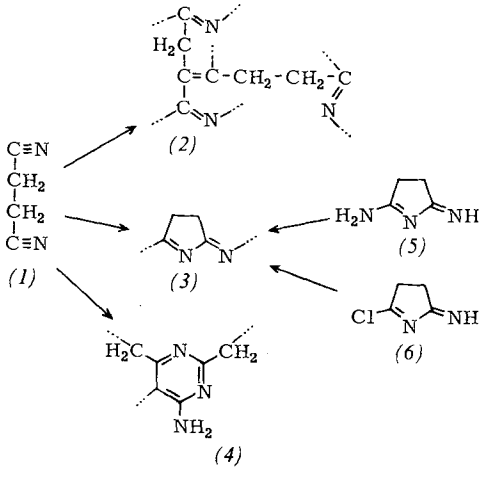
Polymers from Succinonitrile

By *Dieter Wöhrle*[*]

We investigated the catalytic reaction of succinonitrile *(1)* to form polymers, which always contain (—C=N—) bonds.

In the cationic polymerization, *(1)* was allowed to react *e.g.* with metal halides such as $ZnCl_2$ at 180—300 °C. Dark-colored polymers having the crosslinked structure *(2)* were obtained. The investigation of the semiconductor properties showed specific electrical conductivities of $\sigma_{300°K} \leq 1.5 \times 10^{-5}$ ohm^{-1} cm^{-1}. Anionic polymerization could be achieved by reaction of *(1)* in solution *e.g.* in methanol in the presence of $NaOCH_3$ [polymers having the structure *(3)*]. The conductivities are $\sigma_{300°K} \leq 8.5 \times 10^{-8}$ ohm^{-1} cm^{-1}. The bulk polymerization of *(1)* in the presence of potassium *tert*-butoxide, on the other hand, leads to polymers having the structure *(4)* with $\sigma_{300°K} \leq 6.7 \times 10^{-14}$ ohm^{-1} cm^{-1}. In the reaction of *(1)* with Ziegler catalysts such as $TiCl_4/Al(C_2H_5)_2Cl$, dark-colored polymers having the structure *(3)* and with $\sigma_{300°K} \leq 2.7 \times 10^{-9}$ ohm^{-1} cm^{-1} were obtained.

Molecular weight determinations by vapor-pressure osmometry in DMSO gave values of 600—5000 for some



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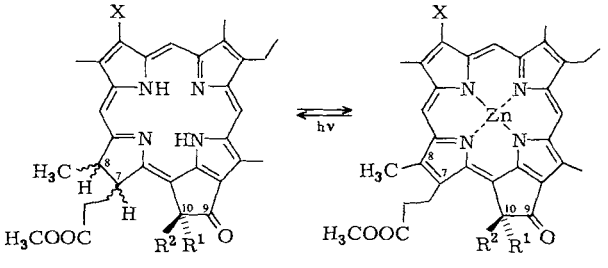
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polymers. It was possible to use mass-spectroscopic sequence analysis for the elucidation of the structures of the polymers. Some of the polymers are stable up to 800 °C under N_2. Polymers having the structure *(3)* could also be prepared by polycondensation from succinimidine *(5)* and 5-chloro-2-imino-α-pyrroline *(6)*.

Preparation and Absolute Configuration of *cis*-Pheophorbides

By *Herbert Wolf* (lecturer) and *Hugo Scheer*[*]

The chiroptic properties of pheophorbides with the *trans* configuration on C-7/C-8 (macrocyclic basic skeleton of chlorophylls a and b) have been investigated in detail[1]. Optically active pheophorbides with the *cis* configuration were not obtainable until now, since the isomerization[2] of natural pheophorbides and the synthesis[3] yielded only the thermodynamically more stable *trans* compounds.



(1) *(2)*

	X	R^1	R^2	Configuration C-7	C-8	C-10
(1a)	Vinyl	$COOCH_3$	OCH_3	*S*	*S (trans)*	*S*
(1b)	Ethyl	$COOCH_3$	OCH_3	*S*	*R (cis)*	*S*
(1c)	Ethyl	$COOCH_3$	OCH_3	*R*	*S (cis)*	*S*
(1d)	Vinyl	H	H	*S*	*S (trans)*	—
(1e)	Ethyl	H	H	*S*	*R (cis)*	—
(1f)	Ethyl	H	H	*R*	*S (cis)*	—
(2a)	Ethyl	$COOCH_3$	OCH_3	—	—	*S*
(2b)	Ethyl	H	H	—	—	—

We succeeded in preparing the *cis*-pheophorbides *(1b)*, *(1c)* and *(1e)*, *(1f)* by "HI isomerization"[4] of the *trans*-pheophorbides *(1a)* and *(1d)* into the pheophorphyrins, whose Zn complexes *(2a)* and *(2b)* were rehydrogenated photochemically to the *cis*-pheophorbides (ethanol/ascorbic acid, 1,4-diazabicyclo[2.2.2]octane, white light). The diastereoisomers *(1b)* and *(1c)* obtained from *(2a)* were separated by thin layer chromatography. The relative configurations were determined from the NMR spectra (proton signals of the pyrrolenine ring), mass spectra (intensity of the $(M-2)^+$ signal resulting from dehydrogenation), and absorption spectra (red shift of the "chlorine band").

The absolute configuration of *(1b)* and *(1c)* on C-7 and C-8 was determined by spectral polarimetry (CE curves at 225, 400, and 535 nm), with reference to the third chirality center C-10, the absolute configuration of which is known[1]. The racemate *(1e)*/*(1f)* obtained from *(2b)* was partly resolved by chromatography on cellulose $2^1/_2$-acetate, and the absolute configuration of *(1e)* and *(1f)* was determined by spectral-polarimetric correlation with *(1b)* and *(1c)*.

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[2] *H. Fischer* and *H. Gibian*, Liebigs Ann. Chem. *550*, 208 (1942); *552*, 153 (1942).
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[4] *H. Fischer, L. Filser*, and *E. Plötz*, Liebigs Ann. Chem. *495*, 1 (1932).

ESR Spectra, Radical Complexes, and Electron Transfer in the Quenching of Photoexcited Rose Bengale by Quinones

By *G. O. Schenck* and *Rudolf Wolgast* (lecturer)[*]

H-bonded radical complexes of substituted hydroxymethyl radicals determine the reaction course *e.g.* of the photoreduction of benzophenone, in which they can be investigated directly by ESR spectroscopy. The quenching of photoexcited dye molecules by quinones which can be detected by the inhibition of the photoreactions of the dye, also occurs *via* radical pair complexes which can be recognized by characteristic reactions and ESR spectra. Thus rose bengale is oxidized in light by oxygen in the presence of duroquinone. The ESR signals from excited rose bengale with duroquinone and 2,3-dimethyl-3-chloroquinone arise only in the absence of oxygen in a predominantly reversible reaction, and differ in their chemical and kinetic behavior, and sometimes also in their hyperfine structure, from the signals of "free" semiquinones.

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The Crystalline State of High Polymers

By *H. G. Zachmann*[*]

Unlike low molecular weight substances, high polymers do not crystallize completely, but consist of a mixture of crystalline and noncrystalline regions, irrespective of the duration of the crystallization process. These regions often form more extensively ordered units (spherulites).

On the basis of a simple two-phase model, it is possible to determine the crystalline content of the samples by various methods, *e.g.* by X-ray studies or from the density. X-ray small-angle scattering gives the mean distance, and hence the size of the crystallites. It is found that the crystalline component and the crystallite size increase with rising crystallization temperature. This clearly shows that the incomplete crystallization is due to kinetic inhibition, which is strongly dependent on the internal mobility and hence on the chemical structure of the chain molecules.

In recent times, interest has been directed mainly at the investigation of the arrangement of the chains in the noncrystalline regions and of the structure of the crystallites.

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Folding of the chains is found on preparation of crystals from the solution. It cannot be definitely established whether the noncrystalline regions of the material crystallizing from the melt also consist of chain folds or loops projecting from the crystallites. It is only known from measurements of the absolute intensity of the small-angle scattering that both the noncrystalline regions and the crystals in many cases do not have the density that they should have in the ideal case. The deviations depend on the chemical structure and on the previous heat treatment. Details on the structure of the crystallites are obtained by evaluation of the intensity and width of the X-ray crystal reflections with the aid of the paracrystal theory. One finds a large number of structural imperfections that, like *e.g.* kinks, are characteristic of high polymers.

Interesting behavior is also observed when high polymers are heated. Instead of a sharp melting point, one observes a melting range, recrystallization processes, or even superheating phenomena, depending on the crystallization conditions. All these results can be readily explained on the basis of a statistical thermodynamics developed specially for chain molecules.

Identification of Amines: Thin Layer Chromatography and Mass Spectrometry of 4-Dimethylamino-3,5-dinitrobenzoyl Derivatives (DADB Amines)

By *Alfred Zeman* (lecturer) and *I. P. G. Wirotama*[*]

For separation and identification, amines were converted into their 4-dimethylamino-3,5-dinitrobenzoyl derivatives (DADB amines). The separation was carried out on silica gel G/Carbowax 400 with the solvent hexane/ethyl acetate (7:3). DADB amines are intensely yellow; compared with the DNP amines[1], which are also deep yellow, they have the advantage of stability to light.

The components separated by thin layer chromatography were identified by mass spectrometry. In the mass spectra of the DADB amines, the molecule-ions and the ions M—ÖH are observed with very high intensity; this provides rapid preliminary information on the molecular weight of the amine. The fragmentation in the case of lower aliphatic amines takes place preferentially in the 4-dimethylamino-3,5-dinitrobenzoyl residue of the molecule; even here, however, the structure of an unknown amine can be largely determined by mass spectrometry. In some cases, *e.g.* for some DADB-iso-alkylamines and DADB-*n*-alkylamines, NMR measurements are also useful. The mass-spectrometric fragmentation of the DADB amines is discussed on the basis of the spectra of numerous derivatives.

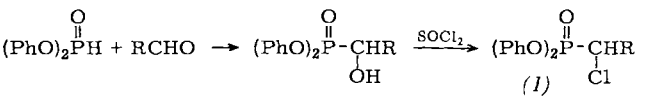
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[1] *A. Zeman* and *J. P. G. Wirotama*, Z. Anal. Chem. *247*, 155 (1969).

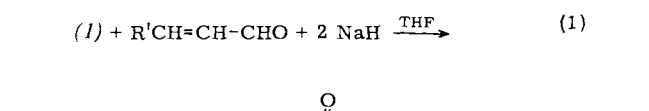
Syntheses of Enynes and Polyacetylenes *via* α-Heterosubstituted Phosphonate Carbanions

By *Hans Zimmer* and *Kenneth R. Hickey*[*]

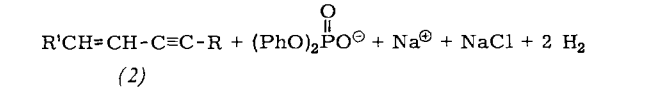
The usefulness of α-heterosubstituted phosphonate esters of type *(1)* as easily accessible starting materials for the synthesis of α-heterosubstituted olefins, enynes, and polyacetylenes *via* a Wittig-Horner-type reaction was demonstrated. The synthesis of the enynes *(2)* is carried out according to Eq. (1).



$$(PhO)_2\overset{O}{\overset{\|}{P}}H + RCHO \longrightarrow (PhO)_2\overset{O}{\overset{\|}{P}}-\underset{OH}{\underset{|}{CHR}} \xrightarrow{SOCl_2} \underset{(1)}{(PhO)_2\overset{O}{\overset{\|}{P}}-\underset{Cl}{\underset{|}{CHR}}}$$



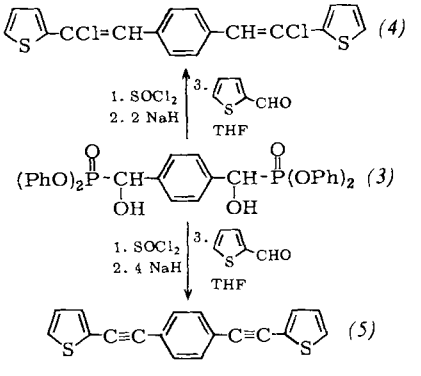
$$(1) + R'CH{=}CH{-}CHO + 2\ NaH \xrightarrow{THF} \qquad (1)$$



$$R'CH{=}CH{-}C{\equiv}C{-}R + (PhO)_2\overset{O}{\overset{\|}{P}}O^{\ominus} + Na^{\oplus} + NaCl + 2\ H_2$$

$$(2)$$

If in this sequence R = *p*-formylphenyl the reaction proceeds *via* the bis(phosphonate) ester *(3)*. In Eq. (2) the reaction with 2-thiophenecarbaldehyde to give the dialkyne *(5)* and the dichlorodialkene *(4)* is given as example.



(2)

The synthesis of several such heterocyclic substituted acetylenes was dealt with. Also, the preparation of an enyne-system-containing natural product was discussed. A mechanism for this reaction was suggested.

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German version: Angew. Chem. *83*, 891 (1971) [VB 314 IE]

Recent topics of petroleum genesis are reported by *A. Shimoyama* and *W. D. Johns*. Clay minerals catalyze the decarboxylation of fatty acids and cracking of the resulting *n*-paraffins. For example, *n*-$C_{21}H_{43}COOH$ and Ca-montmorillonite yielded, besides a kerogen-like main product, all *n*-paraffins C_{16} through C_{28} (other paraffins could not be detected with the analytical procedure used). A crude kinetic analysis of the experiments showed that in geological time this reaction can yield petroleum-like products. [Catalytic Conversion of Fatty Acids to Petroleum-like Paraffins and Their Maturation. Nature Phys. Sci. *232*, 140—144 (1971); 15 references, 3 tables, 4 figures.]

[Rd 408 IE –H]

A brief review of new applications of the Faraday effect in chemistry is given by *A. J. McCaffery*. By Faraday effect (magnetic circular dichroism, MCD) is meant the difference in absorbance of left and right circularly polarized light under the influence of a longitudinal magnetic field. The genesis of MCD is illustrated with simple examples, and a brief account of its theory is given. The measurement of MCD is especially helpful in assignment of absorption bands to certain electronic transitions. Additional applications performed presently and developments possible in the future are considered. [New Applications for Magnetic Circular Dichroism. Nature Phys. Sci. *232*, 137—140 (1971); 35 references, 2 figures.]

[Rd 409 IE –H]

A modern method for the calculation of lattice energies of salts containing complex ions is reported by *H. D. B. Jenkins* and *T. C. Waddington*. A model is used which considers each atom or ion in the crystal as a point charge; the distances are taken from crystal structure data. The charge on the atoms constituting the complex ion appears as a parameter in the calculation. Assuming that the charge distribution in a complex ion does not depend on the details of crystal structure one can eliminate the charge parameter by comparison of polymorphic salts or of series of complex salts with different counterions. Thus, the charge distribution in complex ions can be calculated. [Lattice energies, charge distributions and thermochemical data for salts containing complex ions. Nature Phys. Sci. *232*, 5—7 (1971); 19 references, 2 figures.]

[Rd 410 IE –H]

An account of the stereochemistry of five-coordinate nickel(II) and cobalt(II) complexes is given by *P. L. Orioli*. The relative stabilities of the two ideal configurations (trigonal bipyramid and square pyramid) in different environments are discussed and some factors are mentioned which can effect departures from these ideal geometries. A list is then given of the known complexes of nickel(II) and cobalt(II) with coordination number 5, separated according to their high-spin or low-spin character. [The Stereochemistry of Five-coordinate Nickel(II) and Cobalt(II) Complexes. Coord. Chem. Rev. *6*, 285—308 (1971); 76 references, 7 figures, 13 projection formulas, partly with distances and angles, 6 tables.]

[Rd 411 IE –H]

The assessment and interpretation of properties of transition metal compounds by means of MO calculations is reviewed by *D. R. Davies* and *G. A. Webb*. One chapter deals with the principles of the calculation methods, the models they are based upon, and the different degrees to which they rely on empirical results. Calculations of electronic energy levels in transition metal compounds of different symmetries are then shown; the review concludes with a brief account of the more or less covalent aspects of metal-ligand bonds. [Molecular Orbital Calculations on Transition Metal Compounds. Coord. Chem. Rev. *6*, 95—146 (1971); 267 references, 10 figures, 10 tables.]

[Rd 412 IE –H]

The chemistry of allyl and crotyl Grignard reagents has been reviewed by *R. B. Benkeser*. The author compares the different reaction behavior of these two types of extraordinarily reactive organometallic compounds. Allyl- and crotylmagnesium halides permit introduction of unsaturated C_3- and C_4-chains.

$H_2C{=}CH{-}CH_2{-}MgX$ *(1)* $\qquad$ $H_3C{-}CH{=}CH{-}CH_2{-}MgX$ *(2)*

Steric hindrance of the reaction partner seldom influences the course of the reaction. The review includes: preparation of allyl and crotyl Grignard reagents *(1)* and *(2)*; structure of *(2)*; reactions of *(1)* and *(2)* with carbonyl compounds; exchange reactions; and also addition of *(1)* to azomethines and of *(2)* to olefins. [Synthesis *1971*, 347—358; 93 references, 8 tables, many formulas].

[Rd 413 IE –M]

Methods for the synthesis of polyaminomonosaccharides (di-, tri-, and tetraaminosugars) are reviewed in a paper by *F. J. M. Rajabalee*. The amino functions are usually introduced by N-containing nucleophiles, either directly or *via* cyclic intermediates (epoxides, aziridines, 1,3-oxazolines, 1,3-oxazolones). In many cases nitrosugars are suitable precursors for polyaminosaccharides. [Synthesis *1971*, 359 to 366; 70 references, numerous formulas.]

[Rd 416 IE –M]

Principles of Mass Spectrometry and Negative Ions. By *Charles E. Melton.* Marcel Dekker Inc., New York 1970. 1st ed., v, 313 pp., bound $ 17.75.

A series of books on mass spectrometry have so far been published dealing either with special applications (particularly in organic chemistry) or (insofar as the authors attempt to cover the entire field) presenting the physical fundamentals and the principles of the equipment together with a survey of the various fields of use.

The present book, unlike those that have preceded it, is predominantly of the character of a textbook. The author presents a mathematically immaculate description of the physical principles that are required for an understanding of the function and use of mass spectrometers. Knowledge of vector analysis and of the manipulation of differential equations is necessary for an understanding of the subject matter.

The history of mass spectrometry and the wide field of uses are described briefly, but with many references, in the introductory chapter. Chapters 2 to 8 contain the mathematical description of the physical principles of the following fields: 2. movement of charged particles in electric and magnetic fields, 3. formation of ions, 4. mass separation (analysis), 5. detection of ions, 6. positive ions, 7. negative ions, and 8. secondary reactions. No references for further studies are given in Chapters 2 to 5.

Because of the author's evident delight in the handling of the methods of theoretical physics, the application of the quantum theory in the chapters on positive ions, negative ions, and secondary reactions, *e.g.* in the calculation of effective cross sections for collision phenomena and in pair formation, is not too brief. The appendix contains tables of appearance potentials from investigations with negative ions, secondary reactions of negative ions, and electron affinities of atoms and molecules.

The book should be a useful aid to advanced students of physics and chemistry and to physicists and chemists who wish to familiarize themselves with the field of mass spectrometry. However, it should also find a place in the laboratories of pure and applied specialists.

Karl Heinz Maurer [NB 991 IE]

Carboranes. By *R. N. Grimes.* Academic Press, New York–London 1970. 1st ed., xiv, 272 pp., numerous formulas and tables, bound $ 14.00.

The chemistry of carboranes, which were first reported in 1953, has developed very rapidly during the past 12 years. It now occupies an independent place alongside polyborane chemistry. As in the case of the boranes, the syntheses, the diverse structures, and the bonding (three-center bonds, metal π bonds) in this class of compounds are of interest to the inorganic chemist, the organometallic chemist, and the organic chemist alike. The present book appears at a time when a survey of what has been achieved is of great value.

Following the examination of the most important steric structures and the bonding in the various types of carboranes and of the latest nomenclature, *nido* and *closo* carboranes with small and medium numbers of atoms are discussed.

The treatment concentrates on the preparative field. Most of the book is occupied by the description of preparations and transformations of the three isomeric $C_2B_{10}H_{12}$ carboranes and their derivatives and of the properties of carborane polymers. The alternate conversions of the $C_2B_{10}H_{12}$ isomers into dicarbollides $C_2B_9H_{11}^{2-}$ and the preparation of monocarbapolyborates are then discussed. A section is devoted to the degraded $C_2B_{10}H_{12}$ carboranes with integrated main-group elements (Be, Al, Ga, Ge, Sn, P, As, Sb), and a comprehensive chapter deals with the π complexes of the various carborane anions (dicarbollides $C_2B_9H_{11}^{2-}$, dicarbacanastides $C_2B_8H_{10}^{4-}$, dicarbazapides $C_2B_7H_9^{2-}$) with transition metals.

The up-to-date survey is supplemented by well-chosen literature (472 references). A comprehensive author index and an adequately detailed subject index are added. The author's wish "to summarize the existing literature of carborane chemistry, and to introduce the field to organic chemists and others with little previous knowledge of the boranes" is fulfilled.

Roland Köster [NB 992 IE]

Selective Organic Transformations, Vol. 1. By *B. S. Thyagarajan.* John Wiley and Sons, New York–London–Toronto 1970. 1st ed., 400 pp., numerous formulas, bound £ 9.50.

The first volume of the new series "Selective Organic Transformations", which will appear periodically, has now been published. This series is to present reviews on chemical transformations in which the formation of one of many, usually isomeric reaction products predominates. It is intended to place the description of a plausible reaction mechanism alongside a pure list of preparative and kinetic data.

B. S. Thyagarajan has managed to have the eight reviews in the first volume written by authoritative investigators. More than 150 of the 400 pages are taken up by the nucleophilic addition to acetylene *(S. J. Miller* and *R. Tanaka)* and the stereoselective addition to allenes *(M. C. Caseirio)*. These reactions have only been intensively studied during the last few years; with careful choice of the reactants, they allow the synthesis of olefin derivatives that are otherwise unobtainable.

Two other articles deal with the asymmetric induction in the reduction of carbonyl compounds with hydrides *(S. Yamada* and *K. Koga)* and the asymmetric selection by elimination from cycloalkyl derivatives *(S. Goldberg)*. Both reactions yield the stereoisomers in unequal amounts, since the enantiomer mixtures give transition states having different free energies. The optical induction on addition of hydrides to dissymmetric carbonyl compounds is sufficiently well known through Cram's rule. On the other hand, a new chapter is opened up in asymmetric synthesis by elimination. The reactions involved here are mainly the pyrolyses of sulfoxides, amine oxides, phosphine oxides, and esters in which the loss of a chiral group leads to two "diastereoisomeric" transition states with different energies.

A. T. Bottini discusses the stereoselectivity in the quaternization of tertiary amines, and *R. A. Moss* describes the cycloaddition of carbenes to olefins and subsequent reac-

tions. The last two articles deal with the decomposition of triazolines to form aziridines and imines *(P. Scheiner)*, which is of great interest from the mechanistic standpoint, and oxidation with selenium dioxide, *(R. A. Jerussi)*, which is of immense preparative importance.

It is clear from the diversity of the reaction types discussed that the title of this new series is to be understood in a very broad sense. However, this does not detract from the value of the clearly and comprehensively written individual reviews, and the continuation of the series will be eagerly awaited.

Bernd Giese [NB 993 IE]

Physikalische Grundlagen der Verfahrenstechnik (Physical Fundamentals of Process Engineering). By *P. Grassmann*, Verlag Sauerländer, Aarau and Frankfurt 1970. 2nd ed., 960 pp., figures, bound, DM 128.—.

Ten years ago "Physical Fundamentals of Chemical Engineering" appeared as the first volume of the excellent "Fundamentals of Chemical Technology" series published by Verlag Sauerländer. Now, the second edition has appeared, under a slightly different title. The factual material is presented in twelve main chapters, starting from the fundamentals typical for process engineering from the fields of thermodynamics, physical chemistry, mechanics, fluid dynamics of single-phase and multiphase systems, heat and mass transfer, and mathematics.

Continual use of the work shows that the author has been highly successful not only in his selection of the material but also in combining it into an organic whole. Its relation to the fundamentals has resulted in a pretentious work for scientifically oriented readers, but the author supports his material by careful and readily comprehensible presentation and also by his unambiguous and clear method of writing equations, by graphic illustrations, and by careful cross-indexing and literature references. The reviewer personally found the author's individual style of writing a particular attraction of the book.

The author has not spared himself the trouble of re-formulating a considerable number of chapters in the new edition in order to take into account new developments in those fields. In particular, the sections on "Momentum, heat, and mass transfer" and on "Multiphase flow" have profited from this treatment.

A large number of literature references, have been added, some as recent as 1970, contributing toward the up-to-date nature of the work. The book can be recommended to engineers, physicists, and chemists in the various specialist fields connected with process engineering, as an ever-handy source of advice. In my experience it is also suitable for advanced students as a textbook which can show the relationship between the basic sciences (which otherwise seem isolated) in their application to process engineering problems.

Eckhart Blass [NB 994 IE]

Atomic Absorption Spectroscopy. By *R. J. Reynolds* and *K. Aldous*. With a chapter by *K. C. Thompson*. Charles Griffen & Co. Ltd., London 1970. 1st ed., xii, 201 pp., 29 figures and 6 tables, bound £ 4.50.

This book provides the kind of introduction to the experimental techniques of atomic absorption that an analyst who wanted a quick guide to the essential information for analytical applications would require. Following a very short presentation of the fundamentals, the technical data needed for analysis are given, possible interferences are noted, the selection of suitable flames is discussed, and an attempt is made to clarify essential concepts such as sensitivity, detection limits, precision, *etc.*

The most extensive chapter summarizes the essential data for the atomic absorption determination of 49 elements and the rare earth metals (taken together), in alphabetical order of the elements. The subsequent bibliography contains 74 references, also arranged by elements. In another chapter are given examples of applications: the analysis of biological materials and organic substances, clinical and metallurgical analyses, silicate analyses, *etc.* This is also followed by a suitably arranged bibliography. The book ends with chapters on the characterization of standard equipment, new atomic absorption techniques, and the chapter by *K. C. Thompson* which gives a clear and readily understandable picture of the theoretical foundations. Each chapter is followed by a bibliography. A subject index simplifies the location of specific information. The book will provide the practising analyst with the necessary analytical data in a readily acceptable form, but it also gives the chemical and physical foundations necessary for an understanding of the method.

Hans Massmann [NB 996 IE]

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Methods of Asymmetric Synthesis—Enantioselective Catalytic Hydrogenation

By Yoshiharu Izumi[*]

It is proposed that asymmetric syntheses be divided into enantioselective and diastereoselective syntheses. The enantioselective hydrogenations discussed in the present progress report were catalyzed by Raney nickel that had previously been treated with solutions of optically active compounds. Relationships exist between the enantioselectivity of the catalyst and the structure of the chiral compound used to modify it.

1. Introduction

"Asymmetric synthesis" is still one of the most undeveloped fields of organic chemistry, though most natural products are asymmetric and the enantiomer that occurs in nature is in many cases the only one that acts as a drug, nutrient, or flavoring agent. The development of asymmetric syntheses is of particular interest to branches of industry that produce synthetic natural products such as amino acids.

Studies on asymmetric syntheses are of great importance not only scientifically but also preparatively. They may even help, for example, to elucidate the mode of action of enzymes. Improved knowledge of asymmetric syntheses should also provide an insight into unsolved problems in connection with the origin of life, as well as an answer *e.g.* to the question why all proteins that are important to life consist exclusively of L-amino acids.

We have been concerned in recent years with catalysts for asymmetric hydrogenation. The results are reported briefly in the present article. However, let us first examine the term "asymmetric synthesis".

2. Definitions

The description "asymmetric" is used in two ways. On the one hand, "asymmetric synthesis", is understood to be a reaction in which the enantiomers of a chiral molecule are formed in unequal quantities. On the other, a molecule is described as "asymmetric" if it lacks symmetry elements at least of the second kind.

Nakazaki[1] has referred to the need for a new definition of "asymmetric reactions" based on the concept of chirality[2]. Together with *Nakazaki*, therefore, the present author proposes that "asymmetric syntheses" be divided into enantioselective syntheses and diastereoselective syntheses. In this new classification, most "inductive asymmetric syntheses" are diastereoselective syntheses, while "asymmetric catalytic syntheses", "absolute asymmetric syntheses", and most enzymatic syntheses should be classified as enantioselective syntheses.

2.1. Diastereoselective Synthesis

If a molecule contains a center of chirality and a center of prochirality, the molecule can be divided by a plane in such a way that the parts on either side of the plane are diastereotopically related to each other. If a reaction results in the conversion of the center of prochirality into a new center of chirality, the reagent may attack from either side of this plane, with the result that diastereoisomers are formed[3]. The formation of the diastereoisomers in unequal quantities in such a reaction may be due to differences in the strength with which a catalyst is adsorbed on the two sides of the "diastereotopically reacting" plane of the substrate or to differences in the rate at which a reactant attacks on the two sides of the plane.

We shall refer to reactions of this type as diastereoselective syntheses. For example, in the hydrogenation of 3-ethyl-6-benzylidene-3-methyl-2,5-dioxopiperazine *(1)*[4], a cata-

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Kita-ku, Osaka (Japan)

lyst is adsorbed less strongly on the side of the dioxopiperazine ring (O) on which the ethyl group projects (reverse side in Fig. 1) than on the other side. Hydrogenation thus leads mainly to the product in which the ethyl and benzyl groups lie on the same side of the piperazine ring *(1)* (*cis*-configuration).

A "diastereotopic reaction plane" (P) can also be drawn in the reaction of phenylglyoxyl ester *(2)*, which is shown in Figure 2 in the preferred conformation, with methylmagnesium iodide[5]. In the reaction, the Grignard reagent will preferentially attack the phenylglyoxyl ester from the side opposite the largest substituent L, with preferential formation of the product in which L and the methyl group lie on opposite sides of the plane (P) (*trans*-conformation).

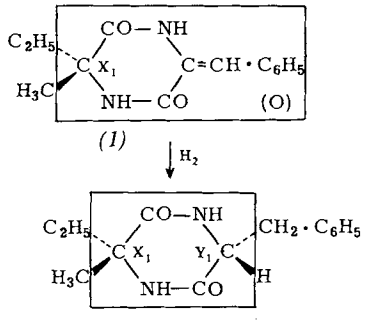


Fig. 1. Diastereoselective hydrogenation on the side of the diastereotopic plane (O) favored by the configuration. x_1 = existing center of chirality, y_1 = induced center of chirality.

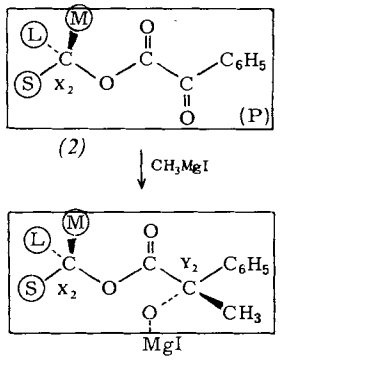


Fig. 2. Diastereoselective synthesis on the side of the diastereotopic plane (P) favored by the conformation. (L), (M) and (S) denote the largest, middle, and smallest substituents respectively. x_2 = existing center of chirality, y_2 = induced center of chirality.

In this type of reaction, the inequality of the quantities of the *cis*- and *trans*-compounds in the product is proportional to the diastereoselectivity of the catalyst or of the reagent. With racemic starting materials, neither a catalyst nor a reactant can induce the preferential formation of one enantiomeric form of the new center of chirality. This can be achieved, however, if optically active substrates are used. If the ligands on the existing centers of chirality x_1 and x_2 are constant, the degree to which x_1 and x_2 influence the stereochemistry of the new centers of chirality y_1 and y_2 depends only on the diastereoselectivity of the catalyst or of the reagent[6]. "Inductive asymmetric synthesis" is thus a special case of diastereoselective synthesis.

2.2. Enantioselective Synthesis

Achiral molecules containing a center of prochirality can be divided by a plane in such a way that the two sides of the plane are enantiotopically related to each other. The attack of a reactant from one side leads to the *S* enantiomer of the new chiral molecule, while attack from the other side leads to the *R* enantiomer[3]. An achiral reactant or an achiral catalyst approaches both sides of the "enantiotopic plane" at the same rate and so yields the racemate. An enantioselective reactant or an enantioselective catalyst, on the other hand, can differentiate between the two sides of the "enantiotopic plane"; the rates of attack on the two sides of the plane are different, and the *R* and *S* compounds are formed in unequal quantities. The difference between the quantities of enantiomers formed depends on the enantioselectivity of the reagent or of the catalyst. A synthesis carried out with an enantioselective reagent or catalyst will be referred to as an "enantioselective synthesis".

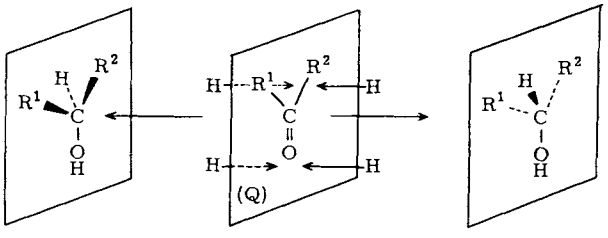


Fig. 3. Enantioselective hydrogenation on the enantiotopic plane (Q).

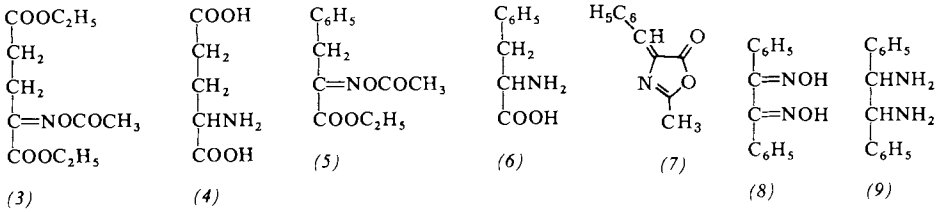
In enantioselective synthesis, the enantioselective action of the catalyst or of the reagent causes the new center of chirality to be formed mainly in the *R* or in the *S* form. Examples of such reactions are the enantioselective hydrogenation described in the present progress report and reactions with chiral Grignard reagents[7].

For example, the enantioselective, modified Raney nickel catalyst (see Section 4 *et seq.*) has two functions; firstly, it catalyzes hydrogenations in the same way as ordinary Raney nickel, and secondly it distinguishes between the two sides of the enantiotopic plane of the substrate. The hydrogenation is due to the metal of the catalyst, and the differentiation between the two sides to the chiral compound adsorbed on the catalyst.

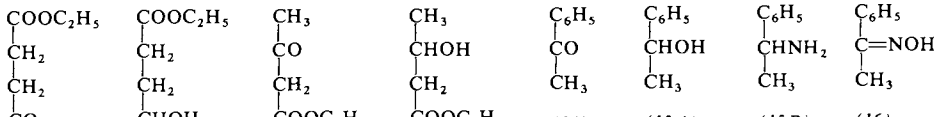
3. Survey

The first enantioselective synthesis with a heterogeneous catalyst was achieved by our research group in 1956 with a silk-palladium catalyst[8–10]. This catalyst enantioselectively hydrogenated derivatives of oximes and oxazolones (Table 1, Part 1).

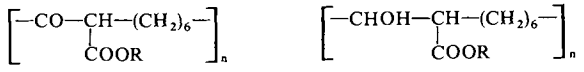
During our investigations on the silk-palladium catalyst and the modified Raney nickel catalyst, *Isoda et al.*[11,12] published a report on enantioselective hydrogenations with Raney nickel. They investigated the hydrogenation of oxazolone and α-oxoglutaric acid derivatives with Raney nickel that had been treated with amino acids (Table 1, Part 2).



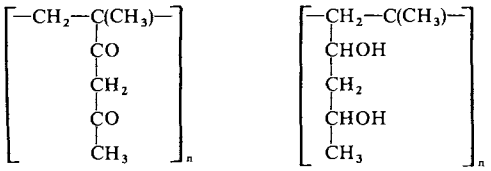
(3) (4) (5) (6) (7) (8) (9)



(10) (11) (12) (13) (14) (15A) (15B) (16)



(17), R = C_2H_5; (18), R = CH_3 (19), R = C_2H_5; (20), R = CH_3



(21) (22)

Table 1. Examples of enantioselective hydrogenations. The italicized figures in brackets in the "substrate" and "product" columns refer to the formulas reproduced here. (R-Ni means Raney nickel.)

Catalyst	Modifying reagent	pH	T (°C)	Hydrogenation (°C)	Substrate	Product	$[\alpha]_D$ (°)	Opt. Yield (%) [a]	Ref.
silk/Pd					*(3)*	*(4)*	+2.25 [b]	6.1	[8]
					(5)	*(6)*	+9.25 [c]	26.3	[8]
					(7)	*(6)*	+12.5 [c]	35.6	[8]
					(8)	*(9)*	+8.75 [d]	—	[8]
R-Ni	(*S*)-tyrosine				*(7)*	*(6)*	−12	36	[12]
					(10)	*(11)*	−0.3	7	[12]
					(3)	*(4)*	−0.1	3	[12]
	(*S*)-glutamic acid				*(10)*	*(11)*	−0.25	6	[12]
	(*S*)-leucine				*(10)*	*(11)*	−0.1	2.5	[12]
	(*S*)-phenylalanine				*(10)*	*(11)*	−0.2	5	[12]
R-Ni	(*S*)-mandelic acid	5.0	20	70	*(12)*	*(13)*	−0.13	0.5	[45]
	(−)-ephedrine	—	20	70	*(12)*	*(13)*	+0.11	0.4	[45]
	L-(+)-*threo*-1-*p*-nitrophenyl 2-aminopropane-1,3-diol	9.5	20	70	*(12)*	*(13)*	−0.10	0.4	[45]
	(2*R*, 3*R*)-tartaric acid	5.0	0	70	*(12)*	*(13)*	−2.02	8.1	[45]
		5.1	20	60	*(14)*	*(15A)*	−0.024	0.96	[45]
		5.1	20	42	*(16)*	*(15B)*	−0.82	2.6	[45]
R-Ni	(*S*)-glutamic acid				*(17)*	*(19)*	+3.12 [e]		[46]
					(18)	*(20)*	+3.75		[46]
	(2*R*, 3*R*)-tartaric acid				*(18)*	*(20)*	+1.42		[46]
	(*S*)-glutamic acid				*(21)*	*(22)*	+6.30		[46]
					(12)	*(13)*	−0.465		[46]

[a] The optical yield is defined as $([\alpha]_D$ (found))/$([\alpha]_D$(lit.)) × 100 [%].
[b] In 2N HCl.
[c] In water.
[d] In ether.
[e] $[\alpha]_D$ values in this column measured at 20°C.

After the investigation of silk-noble metal catalysts[13–18], we turned in 1963 to the enantioselective hydrogenation of methyl acetoacetate with modified Raney nickel. Since then, we have continued our systematic studies on this catalyst[19–40].

In 1964, *Padgett et al.*[41] reported the enantioselectivity of a palladium catalyst on a specially prepared silica gel support (Table 2). The silica gel had been precipitated from sodium silicate with hydrogen chloride in the presence of optically active alkaloids. *Beamer et al.*[42–44] investigated the similar enantioselective hydrogenation of α-methylcinnamic acid and α-acetaminocinnamic acid with palladium catalysts on polyamino acid supports.

The mechanism proposed by *Beamer et al.* for the enantioselective hydrogenation is based on the idea that the catalyst has two kinds of adsorption sites, which differ in their affinity for the two sides of the enantiotopic plane of the substrate. The chiral structure of the polyamino acid used as the support causes the two types of adsorption sites to be formed on the surface of the catalyst in unequal quantities. According to *Beamer*'s view, the enantioselectivity of the catalyst is due to the surface structure of the silica gel, which has been modified in such a way by the precipitation in the presence of optically active alkaloids that the silica gel, like the polyamino acids, can now act as an optically active support for the metal. Ion affinity, dipole interaction, hydrogen bonding, and van der Waals forces are named as playing an important part in the adsorption of the substrate on the catalyst (Fig. 4).

Table 2. Enantioselectivity of a palladium catalyst on an optically active support. α-Methylcinnamic acid is reduced to α-methylphenylpropionic acid, and α-acetylaminocinnamic acid to phenylalanine.

Catalyst \ Substrate	α-Methylcinnamic acid $[\alpha]_D$ (°)	Opt. Yield (%) [a]	α-Acetylaminocinnamic acid $[\alpha]_D$ (°)	Opt. Yield (%) [a]	Ref.
Pd-QN 0.5 SG [b]	+0.87	3.21			[41]
Pd-QDN 0.5 SG [b]	+0.45	1.66			[41]
Pd-CN 0.5 SG [b]	+0.47	1.74			[41]
Pd-CDN 0.5 SG [b]	+0.88	3.25			[41]
Pd-Poly-(*S*)-leucine [c]	−0.536	1.94	−2.6	5.4	[42]
	−3.20	1.18	−2.5	5.16	[44]
Pd-Poly-γ-benzyl-(*S*)-glutamic acid [c]	−1.124	4.15	−2.9	6.0	[43]
Pd-Poly-β-benzyl-(*S*)-aspartic acid [c]	+0.388	1.43	+0.46	0.95	[43]
Pd-Poly-(*S*)-valine [c]	+0.245	0.90	+2.06	4.25	[44]

[a] See footnote [a] in Table 1.
[b] Palladium was deposited on silica gel that had been precipitated in the presence of a sulfate of an organic base (0.5 g of salt based on 42 g of sodium silicate solution). QN = quinine sulfate, QND = quinidine sulfate, CN = cinchonine sulfate, CDN = cinchonidine sulfate.
[c] Palladium was deposited on the polyamino acid indicated.

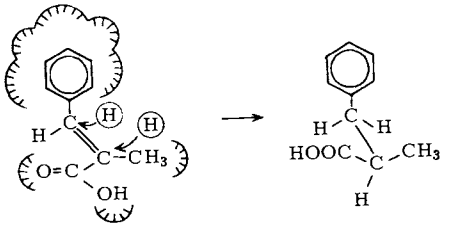


Fig. 4. Course of the enantioselective hydrogenation of α-methylcinnamic acid with palladium on poly-(*S*)-leucine as the catalyst (after a suggestion by *Beamer et al.*) [42—44].

Petrov et al. also investigated modified Raney nickel catalysts (Table 1, Part 3)[45]. *Plate et al.*[46] recently reported the enantioselectivity of modified Raney nickel in the hydrogenation of poly-β-oxo esters and poly-β-diketones (Table 1, Part 4).

Soviet chemists explained the steric effect of a reagent that allows the asymmetric hydrogenation of the substrate on the basis of *Balandin*'s presentation of the multiplet theory of the catalyst[47]. They assume further that the modifying reagent and the substrate are combined in the form of a chelate.

Klabnovskii and *Petrov* suggested that enantioselective hydrogenation on modified Raney nickel proceeds as shown in Figure 5[48]. They assume that the adsorption of the substrate is determined by the stability of the catalyst-

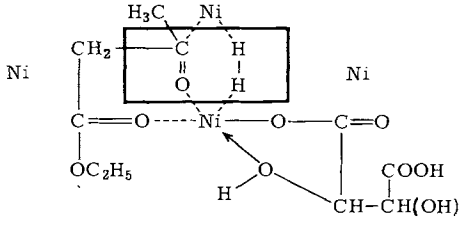


Fig. 5. Enantioselective hydrogenation of ethyl acetoacetate with modified Raney nickel as the catalyst (after a suggestion by *Klabnovskii*) [48].

substrate bond; this bond will be influenced by the chiral structure of the modifying reagent. According to *Plate et al.*[46], the same processes underlie the enantioselective hydrogenation of poly-β-oxo esters or poly-β-diketones.

4. Development of the Modified Raney Nickel Catalyst

In our investigations on enantioselective catalysts, we started by considering the course of enzymatic reactions. We simply assumed at first that the enantioselectivity of enzymatic reactions was due to the asymmetric environment of the protein molecule, and that the chiral product was formed in a "chiral mould" just as a waffle is formed in a waffle iron.

Silk fibroin has a rigid structure, contains no amino acid residues containing sulfur, and can coordinate metal irons. If silk fibroin is boiled with aqueous palladium chloride solution and the silk-palladium complex subsequently hydrogenated, one obtains a palladium catalyst in which the metal is embedded in an asymmetric environment. We achieved the first enantioselective hydrogenation with this catalyst (see Section 3, Table 1). Unfortunately, it was found after a few months that the enantioselectivity of the silk-palladium catalyst is very strongly dependent on the type of silk, and that the results were accordingly not reproducible.

While investigating the reproducibility of the enantioselectivity of the silk-palladium catalyst, we found that the hydrogenation activities of silk-palladium, silk-platinum, and silk-rhodium catalysts are much weaker for the C=O double bond than for other double bonds. To establish whether this behavior was attributable to the silk protein, Raney nickel was treated with aqueous gelatin solution, and the activity of the resulting catalyst for the carbonyl group was tested[49]. It can be seen from Table 3 that the hydrogenation activity of the catalyst for the carbonyl group, as expected, was greatly decreased by this treatment.

At that time we assumed that the active sites on the hydrogenation catalyst behaved differently toward C=O, NO_2, C=C, *etc.* To explain this behavior (see Table 3), the concept of competitive inhibition was applied to these reactions. We assumed that the sites of the catalyst that are active toward the carbonyl group lose their activity when occupied by the carbonyl group of the modifying reagent, which evidently has a greater affinity for these active sites than the carbonyl group of the substrate.

The hydrogenation activities of Raney nickel catalysts modified with amino acids and with chelating agents were also tested on carbonyl, nitro, and C=C double bonds. The results are shown in Tables 3 and 4.

Below 10 °C, the carbonyl group undergoes practically no hydrogenation in the presence of the modified Raney nickel, and the uptake of hydrogen begins only above 60 °C. The hydrogenation activity towards other double bonds, on the other hand, remains unchanged or is even improved by the modification of the catalyst.

Table 3. Hydrogenation activity of modified Raney nickel [49].

Modifying reagent	Hydrogenation activity [a] compared to 2-Butanone at 10 °C	2-Butanone at 60 °C	Allyl alcohol at 10 °C	Nitrobenzene at 10 °C	Nitrobenzene at 40 °C
—	2.0	55	34	9	16
Gelatine [b]	0.5	1.5	38		
(*S*)-Glutamic acid	0	1.5	36		
Glycine	0	3	35		
Glycylglycine	0	2	45		
Sodium hydrogen (*S*)-glutamate				2	8
Disodiumdihydrogen ethylenediamine tetraacetate	0.5	4	37		
Succinic acid	0	3–3.5	25		
Sodium acetate	2	6	—		
Diacetyldioxime	0.5	5.5	50	32	45
Ethylenediamine hydrochloride	0	3	52		

[a] The figure given under "hydrogenation activity" is the percentage of the calculated quantity of H_2 taken up after a certain time (after 30, 5, and 10 minutes respectively) in the cases of C=O, C=C, and NO_2 groups.
[b] Only half of the calculated quantity of H_2 was taken up.

Table 4. Hydrogenation activity of a Raney nickel modified with glutamic acid [49] (R-Ni means Raney nickel.)

Substrate	Hydrogenation activity [a] at 10 °C R-Ni	at 10 °C R-Ni + Glu	at 60 °C R-Ni	at 60 °C R-Ni + Glu
Acetone	5.7	0	55	8
2-Butanone	2	0	20	2
Acetophenone	8	0	120	22
Cyclohexanone	1.8	0	24.3 [b]	7
Allyl alcohol	34	34		
Cinnamic acid	16	16		
Maleic acid	41	63		
Ethyl acrylate	100	100 [c]		
Diethyl maleate	100	100 [d]		
Mesityl oxide [e]	28	14	6	1
Cinnamaldehyde	12.5	0.5	14	

[a] See footnote [a] in Table 3.
[b] Reduction at 80 °C.
[c] Taken up in 3 min.
[d] Taken up in 4 min.
[e] The CO losses in the products were 11% and 3% respectively.

From the above results, we expected that the chirality of an amino acid must take effect if a Raney nickel modified with this amino acid is used as a catalyst in hydrogenations above 60 °C. The Raney nickel catalyst with which the first enantioselective hydrogenation was achieved had been modified with an aqueous solution of (*S*)-glutamic acid.

We have developed the following view on the active sites in modified Raney nickel catalysts. The hydrogenation can take place at any site on the catalyst on which the substrate is adsorbed. The active sites are not specific for the various functional groups such as C=O, NO_2, or C=C. In our view, the active sites on the catalyst surface, *e.g.* dislocations, are capable of functioning even before contact with hydrogen; they initiate the activation of the hydrogen like initiators in a chain reaction.

The position of the modifying reagent on the catalyst surface is determined by the affinity of the reagent for the catalyst on the one hand and the repulsive forces between the reagent molecules on the other. The poisoning of the catalyst can be explained as a special case of modification, *i.e.* poisoning is observed when the repulsive forces between the modifying reagent and the substrate are stronger than the affinity of the substrate for the catalyst.

Since modification of a catalyst often promotes the hydrogenation of one substrate and inhibits the hydrogenation of another (see Tables 3 and 4), the term "modification", is more apt than "poisoning".

5. Preparation of Modified Raney Nickel Catalysts and Determination of the Enantioselectivity

For the investigations discussed here, we prepared Raney nickel from an alloy containing 40% of Ni and 60% of Al. An aqueous solution of the modifying reagent was adjusted

to a predetermined pH value and a predetermined temperature. The freshly prepared Raney nickel was then added, and the mixture was allowed to stand at the same temperature for 1.5 h with occasional shaking. The modifying solution was decanted off, and the catalyst was washed once with water and twice with methanol.

To determine the enantioselectivity of the catalyst, 17 g of methyl acetoacetate was hydrogenated in the presence of the modified Raney nickel catalyst obtained from 1.5 g of alloy. The reaction was allowed to proceed in a shaking autoclave at 60 °C under an initial hydrogen pressure of 80—100 kg/cm^2. After distillation under reduced pressure (b. p. 61—62 °C/12 torr), the optical rotation of the undiluted methyl 3-hydroxybutyrate was measured. The result was taken as the specific rotation, since the specific gravity of the product is approximately 1.0. According to *Levene* and *Haller*[50], $[\alpha]_D^{20}$ of methyl (*R*)-(−)-3-hydroxybutyrate is −20.9°.

The reliability of the results of the enantioselective synthesis improves with increasing purification of the product and with increasing care in the measurement of the optical rotation. Methyl acetoacetate was used as the substrate in most cases, since its hydrogenation product has the following advantages. It can be distilled (with no change in the optical purity); impurities can be easily detected by gas chromatography; its optical rotation is high (see above), and can be measured without dilution of the liquid.

6. Dependence of the Enantioselectivity of the Catalyst on the Modification Conditions

The enantioselectivity of the catalyst is strongly dependent on the temperature and the pH value of the modifying solution. The optimum pH value is 5.0 in the case of acidic modifying reagents and the isoelectric point in the case of monoamino acids (Fig. 6):

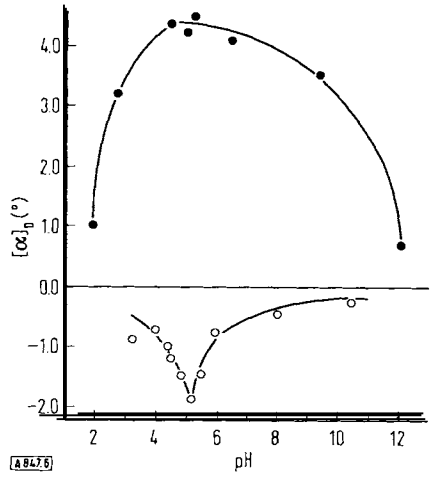


Fig. 6. Enantioselectivity of Raney nickel modified with (*S*)-malic acid and (*S*)-aspartic acid [36] as a function of the pH value of the modifying solution. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.
–○–○– (*S*)-malic acid
–●–●– (*S*)-aspartic acid

On modification with hydroxy acids, the enantioselectivity of the catalyst increases with rising temperature. The temperature dependence is more complicated, however, when the catalyst is modified with amino acids (Fig. 7).

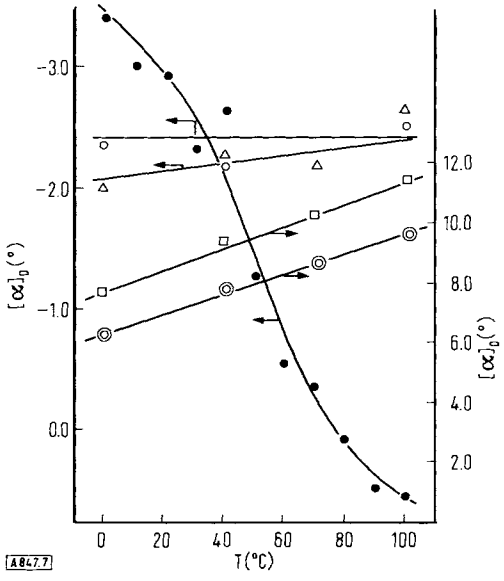


Fig. 7. Enantioselectivity of modified Raney nickel as a function of the temperature of the modifying solution. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate. The right-hand ordinate is valid for the following reagents:
–□–□– (+)-*erythro*-2-methyltartaric acid [27] (modified at pH = 5.0 to 5.2)
–◎–◎– (2*S*,3*S*)-tartaric acid [27] (modified at pH = 5.0—5.2)
The left-hand ordinate is valid for the following reagents:
–△–△– (+)-2-methylglutamic acid [29] (modified at pH = 5.2)
–○–○– (*S*)-valine [20] (modified at pH value of the isoelectric point)
–●–●– (*S*)-glutamic acid [23] (modified at pH = 5.2)

On modification of the catalyst with amino acids such as glutamic acid and leucine, the enantioselectivity changes direction[51] with rising temperature (cf. also Table 6).

7. Conditions for an Enantioselective Modifying Reagent

To give useful enantioselectivity, the modifying reagent must satisfy the following conditions:

1. The modifying reagent must be an optically active compound. Experiments with mixtures of (2*R*, 3*R*)- and (2*S*, 3*S*)-tartaric acid showed that the enantioselectivity of the catalyst varies linearly with the mixing ratio of the modifying reagents[27].

2. If the molecule contains several centers of chirality, it is desirable that their enantioselective effects do not cancel one another out. Part 1 of Table 5 shows the enantioselectivities of some Raney nickel catalysts modified with reagents containing two centers of chirality. (For further examples see [10, 24, 26, 39].)

3. It is desirable that the center of chirality carry one carboxyl group and one amino or hydroxyl group. Part 2 of Table 5 shows the enantioselectivity of Raney nickel catalysts modified with α-substituted succinic acids. A hydroxyl group or an amino group attached to the asymmetric carbon atom gives the catalyst a higher selectivity than a methyl group. As can be seen in Part 3 of Table 5, the amino acids make the catalyst more strongly enantioselective than the corresponding amino alcohols.

Table 5. Examples of enantioselective hydrogenations with Raney nickel modified with compounds of the type R—CR′ X—R″ at 0 °C and at the pH indicated. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.

R	X	R′	R″	Abs. Conf. C_α	Abs. Conf. C_β	pH	$[\alpha]_D^{25}$ (°) [a]	Ref.
$C_2H_5CH(CH_3)$	NH_2	H	COOH	*S*	*S*	5.94	−1.95	[38]
				S	*R*	5.94	−2.13	[38]
$C_2H_5CH(CH_3)$	OH	H	COOH	*S*	*S*	2.9	+0.68	[38]
				S	*R*	2.9	−0.22	[38]
n-$C_3H_7CH(CH_3)$	NH_2	H	COOH	*S*	*S*	6.12	−1.81	[38]
				S	*R*	6.10	−2.42	[38]
n-$C_3H_7CH(CH_3)$	OH	H	COOH	*S*	*S*	2.9	+0.67	[38]
				S	*R*	2.9	+0.22	[38]
iso-$C_3H_7CH(CH_3)$	NH_2	H	COOH	*S*	*S*	5.77	−2.18	[38]
				S	*R*	5.97	−2.50	[38]
iso-$C_3H_7CH(CH_3)$	OH	H	COOH	*S*	*S*	2.9	+0.17	[38]
				S	*R*	2.9	−0.20	[38]
$HOOCCH_2$	NH_2	H	COOH	*S*		5.3	−1.9	[31]
$HOOCCH_2$	OH	H	COOH	*S*		5.0	+4.15	[26]
$HOOCCH_2$	CH_3	H	COOH	*S*		5.0	+0.20	[26]
CH_3	NH_2	H	COOH	*S*		6.0	+0.45 to −0.1 [b]	[37] [40a]
CH_3	NH_2	H	CH_2OH	*S*			−0.04	[37]
$(CH_3)_2CH$	NH_2	H	COOH	*S*		5.9	−2.64	[37]
$(CH_3)_2CH$	NH_2	H	CH_2OH	*S*			−0.15	[37]
iso-C_4H_9	NH_2	H	COOH	*S*		6.0	−1.65	[37]
iso-C_4H_9	NH_2	H	CH_2OH	*S*			−0.25	[37]
$HOOCCH_2CH_2$	NH_2	H	COOH	*S*		5.1	−3.51	[20]
$HOOCCH_2CH_2$	$NHCH_2CH_2CN$	H	COOH	*S*		4.7	−0.10	[20]
$HOOCCH_2CH_2$	$NHCOC_6H_5$	H	COOH	*S*		5.55	−0.67	[20]
$HOOCCH_2CH_2$	$N(CH_3)_2$	H	COOH	*S*		5.01	−0.75	[20]
HOOCCHOH	OH	H	COOH	*R*	*R*	5.0	−6.0	[27]
HOOCCHOH	$OCOC_6H_5$	H	COOH	*R*	*R*	5.2	−2.15	[21]
$HOOCCHOCOCH_3$	$OCOCH_3$	H	COOH	*R*	*R*	5.1	−0.66	[21]
HOOCCHOH	OH	H	COOH	*S*	*S*	5.0	+8.6 [c]	[27]
$H_5C_2OOCCHOH$	OH	H	$COOC_2H_5$	*R*	*R*	5.0	−0.55 [c]	
$HOOCCH_2CH_2$	NH_2	H	COOH	*S*		5.1	−3.51	[19]
$HOOCCH_2CH_2$	NH_2	CH_3	COOH	[d]		6.1	−1.92	[22]
$HOOCCH_2CH_2$	NH_2	$C_6H_5CH_2$	COOH	*R*		7.0	+0.5	[23]
$HOOCCH_2$	NH_2	H	COOH	*S*		5.3	−1.9	[31]
$HOOCCH_2$	NH_2	CH_3	COOH	*S*		7.2	+0.4	[31]
C_2H_5	NH_2	H	COOH	*S*		6.0	−1.46	[31]
C_2H_5	NH_2	CH_3	COOH	*S*		6.0	−0.66	[31]

[a] Values measured at 25 °C in Part 1 of the Table only; otherwise no data available.
[b] See Section 11. [c] Modification at 80 °C.
[d] Dextrorotatory form.

Part 4 of Table 5 shows that substituents on the amino, hydroxyl, or carboxyl group of the modifying reagent reduce the enantioselectivity of the catalyst.

4. A hydrogen atom on the asymmetric carbon atom is essential for the success of the modification. If this hydrogen atom is replaced by other residues, the enantioselectivity of the catalyst decreases (Table 5, Part 5).

8. Relation Between the Structure of the Modifying α-Substituted Acids and the Enantioselectivity of the Catalyst

8.1. Factors that Determine the Direction of the Enantioselectivity

The direction of the enantioselectivity of the catalyst is determined by the absolute configuration of the center of asymmetry C_α of the modifying reagent, which has the general structure RCHX—COOH. The substituent X also

Table 6. Direction of the enantioselectivity in hydrogenations with modified Raney nickel as a function of the absolute configuration on the α-carbon atom of the modifying reagent (modification at about pH = 5). Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.

Modifying reagent	Abs. Conf.	Direction of Enantioselectivity Modification at 0 °C	Direction of Enantioselectivity Modification at 100 °C
(Ala) [a], Cys, Ser, (Thr) [a] or Pro	D	D	L
	L	L	D
Arg, Asp, Ile, Lys, Met, Phe [b], Trp, Val or C_α-alkyl-amino acids	D	L	L
	L	D	D
Glu, Leu	D	L	D
	L	D	L
Hydroxy acids [c]	D	D	D
	L	L	L

[a] See Section 11.
[b] The result published in reference [15] will be reported shortly.
[c] That is, the hydroxy acids corresponding to the above-mentioned amino acids.

influences the direction of the enantioselectivity. Table 5 contains examples in which the direction of the enantioselectivity is reversed when the amino group is replaced by the hydroxyl group. With catalysts modified with L-hydroxy acids, methyl acetoacetate is hydrogenated to methyl (*S*)-(+)-3-hydroxybutyrate; this is not the case on modification with a number of β-substituted hydroxy acids. On the other hand, catalysts modified with L-amino acids generally lead to the (*R*)-(−)-ester (see Table 6).

8.2. Factors that Influence the Degree of Enantioselectivity

The degree of enantioselectivity of the catalyst is determined by the structure of the substituent R. Our investigations on this effect of R lead to the following picture:

1. As described in Section 7 under paragraph 2, a second center of chirality in the substituent has a strong influence of the enantioselectivity of the catalyst. The absolute configuration on the β-carbon atom of an α-hydroxy acid is often of greater importance to the enantioselectivity of the catalyst than the absolute configuration on the α-carbon atom.

2. As can be seen from Figure 8, with amino acids as the modifying reagents, the enantioselectivity of the catalyst increases with increasing chain length. On modification with hydroxy acids, the enantioselectivity of the catalyst decreases with increasing chain length. Figure 9 shows that secondary or tertiary alkyl groups in the modifying reagent influence the selectivity of the catalyst more strongly than primary alkyl groups having the same number of carbon atoms.

3. As is shown in Table 7, hydroxyl, carboxyl, and thiol groups on the β-carbon atom of the modifying reagent strongly influence the enantioselectivity of the catalyst. If the reagent is an amino acid, the substituents not only reduce the selectivity but often reverse its direction, as can be seen, *e.g.* in the examples of modification with serine, threonine, and cysteine. On the other hand, a catalyst treated with α-hydroxy acids substituted in this way exhibits stronger selectivity. From these observations, to-

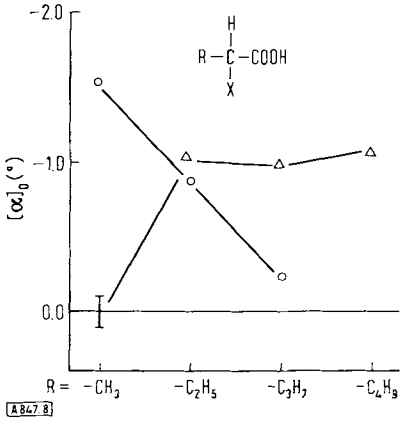


Fig. 8. Enantioselectivity of modified Raney nickel as a function of the substituents on the modifying reagent [28]. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.
-△-△- X = NH_2 (modified at the pH value of the isoelectric point and 0 °C)
-○-○- X = OH (modified at pH = 5.0 and 0 °C)

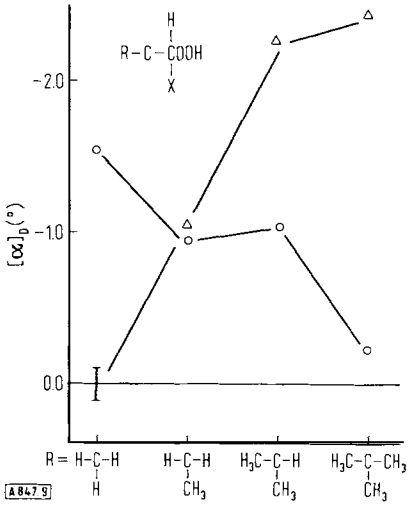


Fig. 9. Enantioselectivity of modified Raney nickel as a function of the substituents on the modifying reagent [28]. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.
-△-△- X = NH_2 (modified at pH = 6 (isoelectric point) and 0 °C)
-○-○- X = OH (modified at pH = 5.0 and 0 °C)

Table 7. Influence of the β-substituent of the modifying reagent of the type RR'CH—CHX—COOH on the enantioselectivity of the Raney nickel catalyst. Modification at 0 °C and the indicated pH value. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.

R	R	X	Abs. conf. C_α	pH	$[\alpha]_D$ (°)	Ref.
H	H	NH_2	*S*	6.0	+0.45 to −0.1 [a]	[37] [40a]
H	H	OH	*S*	5.0	+1.45	[28]
H	CH_3	NH_2	*S*	6.05	−1.05	[28]
H	COOH	NH_2	*S*	5.3	−1.9	[31]
H	COOH	OH	*S*	5.0	+4.15	[26]
H	SO_3H	NH_2	*R*	5.2	−0.2	[36]
H	SO_3H	OH	*R*	5.2	+0.1	[36]
H	OH	NH_2	*S*	6.6	+0.2	[20]
H	SH	NH_2	*R*	7.8	+0.05	[20]
CH_3	CH_3	NH_2	*S*	6.0	−2.31	[29]
CH_3	CH_3	OH	*S*	2.9	+1.05	[21]
CH_3	OH	NH_2	*S* [b]	6	0 to +0.25	[22]
			[c]	6	−0.05 to +0.6	[22]
CH_3	OH	OH	*S* [d]	2.9	+1.30	[26]
			[e]	2.9	+0.50	[26]
COOH	OH	NH_2	*S* [d]	5.5	+0.95	[40b]
			[e]	5.2	−0.50	[40b]
COOH	OH	OH	*S* [d]	5.0	+6.0	[27]

[a] See Section 11.
[b] Threonine.
[c] *allo*-Threonine.
[d] *threo*-Form.
[e] *erythro*-Form.

Table 8. Enantioselectivity in hydrogenations with Raney nickel modified with dipeptide at 0 °C [32]. Substrate: methyl acetoacetate; product: methyl 3-hydroxybutyrate.

Modification		
Reagent	pH	$[\alpha]_D^{20}$
(*S*)-Leucine	7.32	−1.10
(*S*)-Leucyl-glycine	5.72	+1.12
Glycyl-(*S*)-leucine	5.70	−0.41
(*S*)-Leucyl-(*S*)-leucine	5.85	−0.42
(*S*)-Leucyl-(*R*)-leucine	5.80	+1.20
(*S*)-Aspartic acid	4.65	−1.10
Glycyl-(*S*)-aspartic acid	—	−1.47

gether with results mentioned in Section 7 under paragraph 2, it is understandable that the strongest enantioselectivity is obtained by modification with *threo*-tartaric acid [(2*S*, 3*S*)].

4. If the amino acid or α-hydroxy acid with which the catalyst is modified contains a sulfonic acid group, the enantioselectivity is decreased (Table 7).

5. If dipeptides are used instead of amino acids for modification of the catalyst, the relation between structure and enantioselectivity becomes more complicated. As can be seen from Table 8, the direction of the enantioselectivity is generally determined by the center of chirality of the C-terminal amino acid.

9. Durability of the Catalyst

The modified Raney nickel retains its enantioselectivity for a very long time[27]. In a series of experiments, freshly prepared modified catalyst was used for the hydrogenation of methyl acetoacetate, recovered, and used again. The $[\alpha]_D$ values of the methyl 3-hydroxybutyrates obtained in experiments with fresh catalysts and with catalysts that had been recovered once, twice, three times, four times, and five times were −6.22, −6.30, −6.09, −6.01, −6.25, and −6.19° respectively. The modifying reagent was (2*S*,3*S*)-tartaric acid.

10. Substrates for Hydrogenations with Modified Raney Nickel

The best substrates for modified Raney nickel are β-oxo esters and β-diketones. Monoketones are also enantioselectively hydrogenated to secondary alcohols, but the optical yields are low, as can be seen from Table 9.

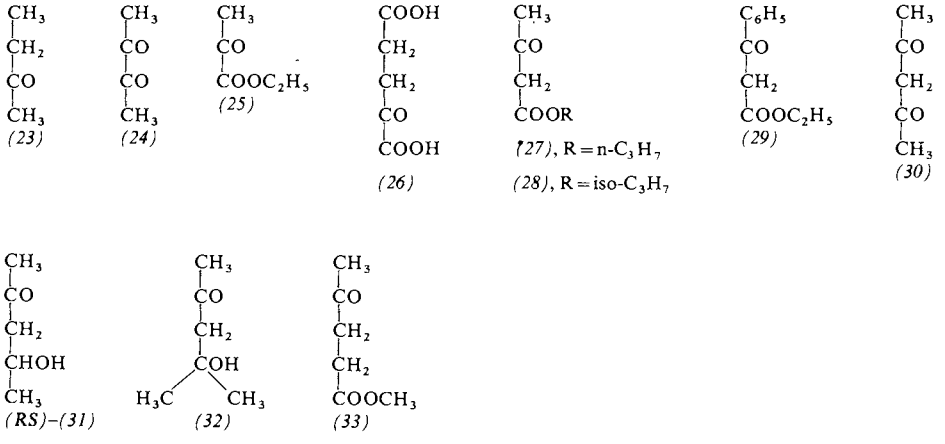


Table 9. Examples of enantioselective hydrogenations with modified Raney nickel. The italicized numbers in brackets in the "substrate" column refer to the formulas reproduced above, or, in the case of numbers lower than *(23)*, to the formulas given with Table 1 [30].

Substrate		Catalyst				Product		
Cpd.	Amount (g)	Alloy Amount (g)	Modification Reagent [a]	pH	*T* (°C)	$[\alpha]_D$ (°)	Abs. Conf.	Opt. Yield [b]
(23)	14	1.5	W	5.10	100	+1.0	*S*	7.7
(23)	10	1.5	G	5.05	0	−0.11	*R*	0.8
(14)	18	1.5	G	5.16	0	+0.93	*R*	2.1
(24)	15	1.5	W	5.0	0	−0.06	*R*	0.5
(25)	5	0.5	W	5.0	0	+0.26	*S*(L)	2.5
(26)	7	1.5	G	5.1	0	0	—	0
(10)	10	1.5	W	5.2	100	0	—	0
(10)	10	1.5	W	5.0	100	0	—	0
(12)	20	1.5	W	5.1	0	−2.97	*R*(D)	18
(27)	22	1.5	W	5.1	0	−2.28	*R*(D)	16
(28)	14	1.0	W	5.0	0	−0.76	*R*(D)	5
(29)	12	1.0	G	5.12	0	+1.90	*R*(D)	8.3
(30)	18	1.5	W	5.0	0	−14.83	—	—
(31)	5	1.5	W	5.0	0	−1.15	—	—
(32)	13	1.5	G	5.0	0	0	—	0
(33)	10	1.0	W	5.2	0	−0.40	*R*(D)	3.1

[a] W = (2*R*, 3*R*)-tartaric acid, G = (*S*)-glutamic acid.
[b] See footnote [a] in Table 1.

11. Dependence of Enantioselectivity of Catalyst on Hydrogenation Conditions

The hydrogenation temperature has no influence on the enantioselectivity of the catalyst above 60 °C. Below 60 °C, however, the catalysts exhibit practically no hydrogenation activity and practically no enantioselectivity.

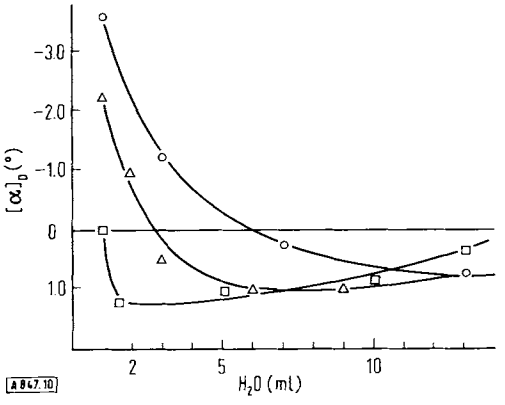


Fig. 10. Effect of water on the enantioselectivity of a modified Raney nickel catalyst. The quantities of water are based on 17 g of the substrate methyl acetoacetate [40a].
-○-○- (*S*)-glutamic acid (modified at pH = 5 and 0 °C)
-△-△- (*S*)-valine
-□-□- (*S*)-alanine (both modified at the pH of the isoelectric point and 0 °C)

Any trace of impurities, particularly carboxylic acids, either in the substrate or in the solvent, affects the enantioselectivity of the catalyst[40]. This effect is more pronounced with amino acids as the modifying reagents than with hydroxy acids. In the former case, as can be seen from Figure 10, the direction of the selectivity may even be reversed in the presence of water.

12. Hypothesis on the Course of the Enantioselective Hydrogenation

As was mentioned in Section 2.2, the enantioselective hydrogenation is made possible by a preceding enantioselective adsorption of the substrate on the catalyst surface. To explain the enantioselective adsorption, the adsorption process is broken down into three steps, as shown in Figure 11. From the fact that β-diketones and β-oxo esters give the best results in enantioselective hydrogenation with modified Raney nickel, it can be concluded that adsorption of the carbonyl groups on the catalyst surface to form a chelate structure plays an important part in the hydrogenation. Thus the Raney nickel catalyst itself has the ability to adsorb carbonyl compounds selectively in the direction of the C=O axis.

The modification of the catalyst with an optically active compound decides whether the catalyst attacks the substrate from the re side or the si side[3]. Since the z axis of the substrate is fixed by the catalyst surface, the modification of the catalyst must produce the selectivity for the x and y axes of the substrate. There are two possible explanations for the production of the enantioselectivity on modification: 1. As proposed by *Beamer*[44], there are two types of

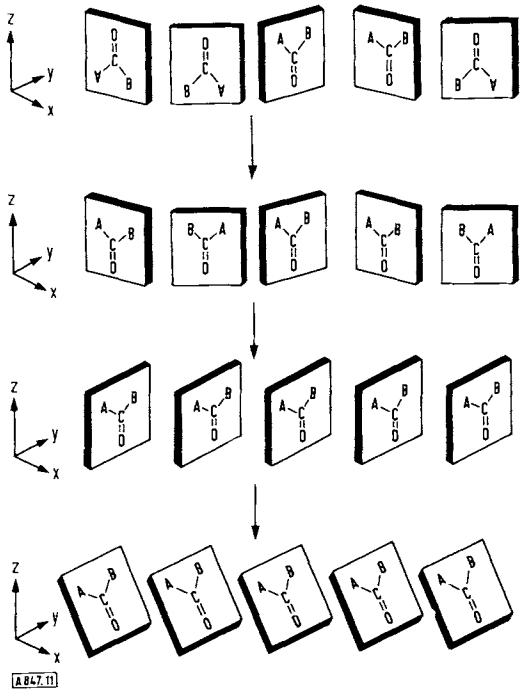


Fig. 11. Enantioselective adsorption of a ketone on the surface of a modified Raney nickel catalyst (schematic). The z axis is perpendicular to the surface of the catalyst.

sites on the untreated catalyst, one of which produces the *S*-form and the other the *R*-form, and one type is blocked or poisoned as a result of the modification, 2. The enantioselective site is formed by the combined effect of the catalyst surface and the modifying reagent.

Experimental results support the second possibility. If the enantioselectivity of the catalyst were due to the first process, a double modification, first with (*S*)- and then with (*R*)- or first with (*R*)- and then with (*S*)-glutamic acid, should deactivate both types of enantioselective sites on the catalyst. However, the enantioselectivity of the catalyst depends only on the last modifying reagent used[19].

It is clear from the facts described above that the selectivity is produced by the modifying reagent adsorbed on the catalyst. The adsorbed reagent is in adsorption equilibrium with its solution.

In the present review, it has been possible to describe only the most important results obtained with Raney nickel catalysts, mainly modified at pH = 5 and 0 °C. For further results and detailed discussions, the reader is referred to the original literature.

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[51] Note on the concept of enantioselectivity. In the discussion of enantioselectivity, two factors must be considered: (i) the numerical value of the optical rotation of the enantioselectively hydrogenated product and (ii) the sign + or − associated with the absolute configuration of the product. Whereas the first factor is important in the discussion of the optical yield, the second factor indicates the "direction of the enantioselectivity".

Active Transport of Na^+ and K^+ through Animal Cell Membranes[**]

By Wilhelm Schoner[*]

The transport of Na^+ out of the cell and K^+ into the cell against a concentration gradient is catalyzed by a ($Na^+ + K^+$)-activated ATPase. The way in which the cations pass through the cell membrane has not yet been elucidated. Studies on the ATP hydrolysis revealed a Na^+-dependent phosphorylation of the enzyme protein; the conformation of the enzyme also appears to change. The energy required for transport of the cations against their concentration gradients is probably provided by K^+-dependent hydrolysis of the enzyme-bound phosphate. The enzyme can synthesize ATP from inorganic phosphate and ADP on reversal of the cation concentration gradient. By keeping the enzyme in a particular conformation, the cardiac glycoside ouabain specifically inhibits the Na^+ pump.

1. Introduction

The distributions of the monovalent cations sodium and potassium inside and outside living cells are usually different[1]. The potassium concentration is generally high and the sodium concentration low inside cells, while the situation is reversed outside the cells[1-3]. If the cell dies, or if its metabolism is blocked by cell poisons or by supercooling, the distributions become the same[4-7].

1.1. Action of Sodium and Potassium Ions on Metabolism[2, 3]

Potassium ions increase, among other things, the respiration in muscle, kidney, adipose tissue, and erythrocytes[8-13], glycolysis and lipolysis[14-19], protein synthesis[20], and acetylcholine synthesis[21]. Sodium ions have an inhibitory effect on the same metabolic processes.

The reason for the antagonistic effects of these two cations has been found in some cases to be an activating effect of potassium ions and an inhibitory effect of sodium ions on enzymes[19, 22-24]. Since the cell membrane is permeable to both cations[25, 26], K^+ must be pumped into the cell and Na^+ out of the cell ("Na^+ pump") in order to maintain a metabolism in the cell that is largely independent of the composition of the extracellular electrolytes.

1.2. Physiological Importance of the Active Transport of Na^+ and K^+

By establishing a difference in the distributions of sodium and of potassium ions between the interior and the exterior of the cell, the Na^+ pump also provides the conditions through which the stimulation of nerve and muscle is possible[27-31]. It can be assumed from investigations on the syndrome of hereditary spherocytosis of the erythrocytes[32-34] that the osmotic pressure of the cells is probably kept constant by active transport of Na^+ and K^+, *i.e.* transport against the concentration gradient. The active transport of Na^+ and K^+ is also the driving force for the movement of NaCl and water in the reabsorption of primary urine in the tubular cells of the kidney[35, 36] and in the secretion of saliva and of pancreatic juice[37]. An active Na^+ pump is also essential to the absorption of glucose and amino acids through the mucous cells of the small intestine and the tubular cells of the kidney (general reviews in[5, 28, 30, 34, 38-42]).

2. Properties of the Na^+ Pump

Detailed information about the properties of the Na^+ pump has been obtained in particular from studies with isolated perfused squid giant axons and with erythrocytes loaded by reversible hemolysis[43]. As was shown by these investigations, the energy for the transport of cations against the concentration gradient is obtained by hydrolysis of adenosine triphosphate (ATP)[44-52]. The binding site of ATP is located on the inside of the cell membrane, where the reaction products adenosine diphosphate (ADP) and inorganic phosphate (P_i) are also liberated[51, 53, 54].

The active transport of sodium into the extracellular space is coupled with the transport of potassium into the intracellular space[44, 55-57]. Sodium ions can be taken up by the pump only on the inside of the membrane[58-60]; on the outside of the membrane, they act as antagonists of the potassium ions that are necessary for their transport[32, 60-62]. However, this function of the potassium ions on the outside of the membrane can also be taken over by other alkali metal ions[57-63].

Cardiac glycosides specifically inhibit the Na^+ pump on the outside of the cell membrane[51, 64-66], whereas they have no effect on the inside[67].

These observations can be combined in a kinetic model of the active transport of Na^+ and K^+ developed by *Shaw*[55] (Fig. 1). Na^+ on the inside of the cell membrane is bound to a carrier, and migrates with the latter through the cell membrane. On the outside of the membrane the carrier

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gives up Na^+ and becomes the K^+ carrier. The K^+ carrier charged with K^+ passes to the inside of the cell membrane, where it gives up K^+. The K^+ carrier is then converted back into an Na^+ carrier by an ATP-dependent reaction.

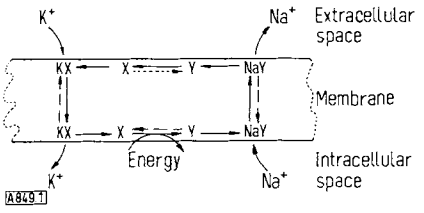


Fig. 1. Kinetic model of the coupled transport of Na^+ and K^+ in opposite directions through the cell membrane (after *Shaw* [55]). X = potassium carrier, Y = sodium carrier.

In agreement with this model, it was shown for the squid giant axon that the transport of sodium ions out of the cell is linked with the absorption of an equal number of potassium ions into the cell. According to *Baker* and *Shaw*[68,69], approximately three sodium ions are transported out of the cell and three potassium ions into the cell per mole of ATP hydrolyzed. However, *Garrahan* and *Glynn*[70] and *Post et al.*[54,56,71] found a ratio of only $3\,Na^+/2\,K^+$ per mole of ATP hydrolyzed for human erythrocytes. Evidently the Na^+ transport can be partially uncoupled from the K^+ transport. Investigations carried out in recent years have shown that uncoupling occurs when the intracellular ATP/ADP or ATP/P_i ratios are low[72-74].

2.1. ATP Synthesis by Reversal of the Na^+ Pump

The coupling of the active transport of Na^+ with the K^+ transport and the dependence of this process on the hydrolysis of ATP raises the question whether reversal of the Na^+ pump can lead to an ATP synthesis. This question has been largely answered by investigations on human erythrocytes. The Na^+ pump was reversed by incubating red blood cells, which had been preloaded with ATP, ADP, inorganic [^{32}P]phosphate and K^+, in Ringer's solution containing no K^+ but Na^+ in high concentrations. Under these conditions radioactive phosphate is incorporated into ATP[75-82]. This process is inhibited by ouabain, the specific inhibitor of the Na^+ pump. The possibility that the labeling of the ATP with $^{32}P_i$ took place *via* the substrate chain phosphorylation in the glycolysis, and is thus independent of the reversal of the Na^+ pump, was ruled out[75,76]. The synthesis of ATP by reversal of the Na^+ pump was found to be favored by steep concentration gradients of Na^+ and K^+ and by low $[ATP]/([ADP]\cdot[P_i])$ ratios[78-85]. Preliminary stoichiometric studies have shown that one molecule of energy-rich phosphate is formed for the efflux of two to three potassium ions[77,80]. The intracellular ATP synthesis by reversal of the Na^+ pump stops when the potassium concentration in the extracellular space and the sodium concentration in the cell rise above 10 mmole/l[78,79,83].

3. ($Na^+ + K^+$)-Activated ATPase and the Na^+ Pump

The cell membranes and microsomes of cells with an active Na^+ pump contain an ATP-hydrolyzing enzyme system, which is activated by the simultaneous presence of sodium and potassium ions. An ($Na^+ + K^+$)-activated ATPase found in the cell membranes of crab nerve was first described in 1957 by *Skou*[86]. The enzyme has now been detected in all the tissues in which active transport of Na^+ and K^+ occurs that can be inhibited by ouabain[34,36,38-40,87,88]. *Bonting et al.*[88], in particular, investigated the relation between the active Na^+ pump and ($Na^+ + K^+$)-activated ATPase. Though the pump activities may differ very widely in some cases, a constant ratio of cation flux/($Na^+ + K^+$)-ATPase activity, based on a membrane area of 1 cm^2, is found in all tissues. These findings show that the ($Na^+ + K^+$)-activated ATPase corresponds to at least a part of the Na^+ pump.

3.1. Properties of ($Na^+ + K^+$)-Activated ATPase

($Na^+ + K^+$)-activated ATPase is a structure-bound enzyme. Attempts to separate the enzyme from the cell membrane with proteases[89,90] or phospholipase[89,91-93] or by physical treatment[89] were unsuccessful. The enzyme has, however, been converted into a pseudo-solution by treatment of the cell membranes with detergents[94,95]. Purification of the enzyme from inactive accompanying proteins and from a soluble ATPase that is dependent only on Mg^{2+} can be achieved by differential centrifugation to obtain the cell membranes, treatment with salts and detergents, and aging[34,38,89].

For optimum activity, the ($Na^+ + K^+$)-activated ATPase requires the *simultaneous* presence of Mg^{2+}, Na^+, and K^+. With magnesium ions alone, the enzyme exhibits only weak activity. The additional presence of one of the monovalent

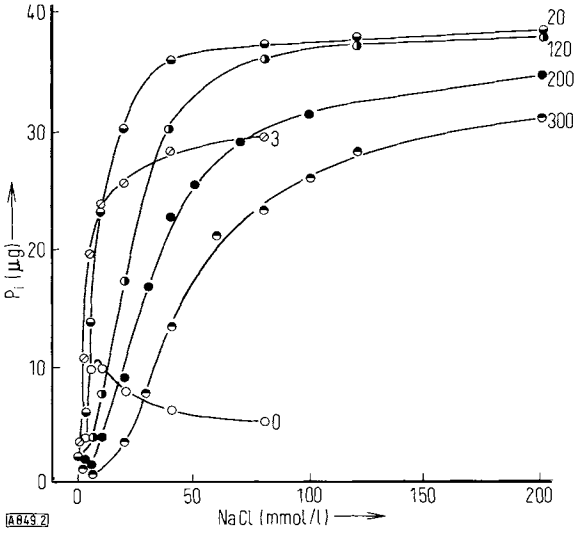


Fig. 2. Na^+ dependence of the activation of the ($Na^+ + K^+$)-activated ATPase of crab nerve at various K^+ concentrations; Mg^{2+} concentration: 6 mmole/l (from *Skou* [86]). Ordinate: relative rate of liberation of phosphate from ATP, expressed as µg of P_i per unit time. The figures by the curves are the K^+ concentrations in mmole/l.

cations Na^+, K^+, Rb^+, Cs^+, Li^+, and NH_4^+ increases the hydrolysis of ATP[86]. A considerable further activation is observed when sodium ions are added to the reaction mixture that already contains magnesium and potassium ions (Fig. 2). Sodium ions are absolutely essential for this additional activating effect, and cannot be replaced by other monovalent cations. Potassium ions, on the other hand, can be replaced by other alkali metal or ammonium ions.

The optimum enzyme activity of the $(Na^+ + K^+)$-activated ATPase is determined by the Na^+/K^+ ratio, and is usually reached at a concentration of 100 mmole/l of Na^+ and 20 mmole/l of K^+ (+6 mmole/l of Mg^{2+}) (Fig. 2). In contrast with the Na^+ pump, however, the enzyme system exhibits no pronounced adenine-specificity[89, 96, 97]; besides ATP, other nucleoside triphosphates also slowly undergo $(Na^+ + K^+)$-dependent cleavage[98]. The use of other nucleoside triphosphates as energy sources for the Na^+ pump cannot be detected with certainty in the models used for transport studies; the test systems are probably not sensitive enough. The membrane-bound enzyme, like the Na^+ pump, is inhibited by ouabain, oligomycin, and fluoride and calcium ions[99–101]. The molecular weight of the $(Na^+ + K^+)$-activated ATPase has been calculated from the inactivation of the enzyme by X-rays on the basis of the "target theory" to be $2.5 \times 10^5 - 5.0 \times 10^5$[102, 103].

3.2. Course of ATP Hydrolysis

When the $(Na^+ + K^+)$-activated ATPase is incubated with terminally labeled [^{32}P]-ATP, $(Mg^{2+} + Na^+)$-dependent incorporation of radioactive phosphate is detected in the denatured enzyme obtained by precipitation with acid[96, 98, 104–113]. On addition of potassium ions to the *native* enzyme that has already been phosphorylated in the presence of magnesium + sodium ions, the incorporated radioactivity is rapidly lost (Fig. 3). This observation suggests that the $(Na^+ + K^+)$-activated hydrolysis of ATP proceeds in at least two steps [equations (1) and (2), E = enzyme]:

$$ATP + E \xrightleftharpoons{Mg^{2+},\,Na^+} E \sim P + ADP \qquad (1)$$

$$E \sim P + H_2O \xrightarrow{K^+} E + P_i \qquad (2)$$

The function of the sodium ions in the phosphorylation reaction cannot be taken over by other cations. The activating effect of the potassium ions on the liberation of phosphate, on the other hand, is also exhibited by other alkali metal ions and by ammonium ions[105].

The degree of phosphorylation of the membrane-bound enzyme protein is determined by the specific enzyme activity of the $(Na^+ + K^+)$-activated ATPase preparation, the Na^+ concentration, the concentrations of Mg^{2+} and ATP, and their ratio[98, 105, 110, 111]. Other nucleoside phosphates besides ATP can act as phosphate donors in the phosphorylation reaction (Fig. 3)[87, 98, 110, 114].

The Na^+-dependent phosphorylation reaction has been found in all membrane preparations with an $(Na^+ + K^+)$-activated ATPase[112, 113]. This is significant in that the preparations of this membrane-bound enzyme obtained so far are still relatively impure. The results of comparative kinetic studies on the rates of the $(Na^+ + K^+)$-activated hydrolysis of ATP and of the Na^+-dependent phosphorylation reaction agree with the assumption that the concentration of a phosphorylated intermediate determines the rate of liberation of phosphate[105, 108–110].

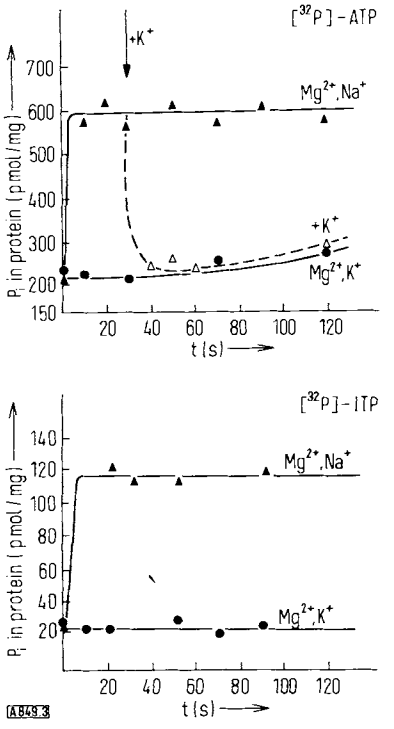


Fig. 3. Kinetics of the Na^+-dependent uptake and release of phosphate by the $(Na^+ + K^+)$-activated ATPase on incubation with [^{32}P]-ATP (top) and [^{32}P]-ITP (bottom). 30 seconds after the start of phosphorylation (arrow), 5 µmole of KCl were added to the native enzyme (after *Schoner et al.* [98]).

Corresponding to the assumption that the $(Na^+ + K^+)$-activated hydrolysis of ATP consists of an Na^+-dependent phosphorylation reaction [eq. (1)] and a K^+-dependent phosphatase reaction [eq. (2)], an *Na^+-dependent ATP-ADP transphosphorylation reaction* has been demonstrated in the enzyme preparations[115–120]. This reaction becomes noticeable only after a soluble enzyme has been separated out that catalyzes a Mg^{2+}-dependent ATP-ADP transphosphorylation[118]. This adenine-unspecific ATP-ADP transphosphorylation reaction does not take part in the $(Na^+ + K^+)$-activated hydrolysis of ATP[118]. The Na^+-dependent ATP-ADP transphosphorylation most probably participates in $(Na^+ + K^+)$-activated ATP hydrolysis. This reaction has a Mg^{2+} optimum of 0.1 to 0.2 mmole/l[115–119], thus contrasting with the Na^+-dependent phosphorylation reaction and the $(Na^+ + K^+)$-activated hydrolysis of ATP, which reach their optimum rate at Mg^{2+} concentrations of 3 mmole/l. However, the optimum Mg^{2+} concentration for the Na^+-dependent ATP-ADP transphosphorylation reaction is shifted towards higher values (3 mmole/l)[104] if the second step [eq. (2)], *i.e.* the K^+-dependent liberation of protein-bound phosphate, is blocked by pretreatment of the ATPase with *N*-ethylmaleimide (NEM) or by the addition of ouabain or oligomycin[95, 105, 110]. Simultaneously the

Na^+-dependent [^{14}C]-ADP-ATP exchange activity increases[115,116]. Both the Na^+-dependent phosphorylation and the Na^+-dependent ATP-ADP transphosphorylation exhibit half-maximal activation by sodium ions at the same concentration[116,117]. Calcium ions inhibit the Na^+ pump[49], the $(Na^+ + K^+)$-activated ATPase[99-101], the Na^+-dependent phosphorylation[105], and the Na^+-dependent ATP-ADP transphosphorylation[115].

On the basis of these similarities, it is assumed that the Na^+-dependent ATP-ADP transphosphorylating enzyme is part of the $(Na^+ + K^+)$-activated ATPase. However, the question of the nucleotide specificity still remains to be answered. In contrast with the $(Na^+ + K^+)$-activated hydrolysis of ATP and the Na^+-dependent phosphorylation[87,98,110], the Na^+-dependent ATP-ADP transphosphorylation is adenine-specific[115,116,119].

The enzyme that catalyzes this last reaction has recently been brought into solution[121]. This agrees with the assumption that $(Na^+ + K^+)$-activated ATPase is a multienzyme complex, the Na^+-dependent phosphorylation being catalyzed by a different enzyme unit from that involved in the K^+-dependent phosphatase step[122].

No P_i-ATP exchange has so far been observed with the $(Na^+ + K^+)$-ATPase preparations[97,115]. This exchange should be detectable, since an incorporation of radioactive phosphate into ATP that could be inhibited by ouabain was demonstrated for erythrocytes under conditions which lead to a reversal of the Na^+ pump[75-80,82]. The failure to detect a P_i-ATP exchange is probably due to the fact that no cation concentration gradient can be built up between the inside and the outside of the membrane fragments in the enzyme suspensions.

Two states of the phosphorylated intermediate were postulated by *Fahn et al.*[114,115] on the basis of the difference in the Mg^{2+} optima of the Na^+-dependent ATP-ADP transphosphorylation on the one hand and for the Na^+-dependent phosphorylation and the overall reaction of the $(Na^+ + K^+)$-activated ATPase on the other. *Post et al.*[123,124] were able to confirm this assumption further by kinetic studies on the reactivity of the phosphorylated intermediate toward ADP and K^+. Thus the following steps are involved in the $(Na^+ + K^+)$-activated hydrolysis of ATP (Fig. 4)[123]. Sodium ions are bound by the enzyme in the conformation E_1 in which it has a high affinity for Na^+[117]. The portion of the enzyme to which Na^+ is bound can be phosphorylated (step I). This reaction corresponds to the Na^+-dependent ATP-ADP transphosphorylation detected for the native enzyme at low Mg^{2+} concentrations (0.1 mmole/l)[115]. At higher Mg^{2+} concentrations (3 mmole/l), the phosphorylated enzyme passes from the conformation E_1-P into the state E_2-P (step II). This leads to inhibition of the Na^+-dependent ATP-ADP transphosphorylation; the phosphorylated intermediate can no longer react with ADP[115,123]. If the transition from E_1-P to E_2-P is inhibited by oligomycin, *N*-ethylmaleimide (NEM), or BAL arsenite[96,105,110], the Na^+-dependent ATP-ADP transphosphorylation is accelerated and can now also be detected at an Mg^{2+} concentration of 3 mmole/l[116,117]. On inhibition of the $(Na^+ + K^+)$-activated ATPase by oligomycin and NEM, the enzyme is no longer dephosphorylated on addition of K^+, though dephosphorylation does occur on addition of unlabeled ADP[123,124]. If the native enzyme is phosphorylated at high Mg^{2+} concentrations so that the formation of E_2-P is favored, the phosphate can be liberated only by addition of K^+ (step III), but not by addition of ADP[123].

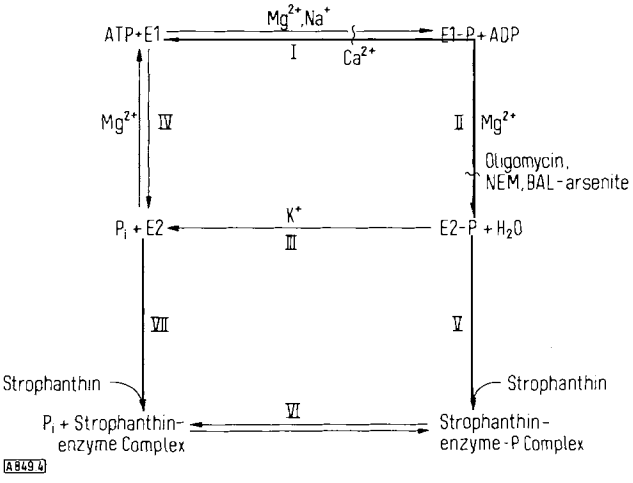


Fig. 4. Reaction steps in the $(Na^+ + K^+)$-activated hydrolysis of ATP (numbered I to VII, E = enzyme). Wavy lines show the points of attack of inhibitors. BAL arsenite = 2,3-dimercaptopropanol + arsenite in equimolar amounts (strophanthin = ouabain).

The phosphorylated enzyme seems to be converted into another modification in the presence of the specific inhibitor ouabain (strophanthin) (step V). *Post et al.*[123,124] showed that the phosphorylation of the enzyme with [^{32}P]-ATP in the presence of strophanthin leads to a phosphorylated product that can no longer be hydrolyzed by the addition of K^+. The formation of this modified form of the phosphorylated enzyme is prevented if the ATPase is pretreated with NEM. On addition of ouabain and magnesium ions to the unphosphorylated enzyme, it can no longer undergo Na^+-dependent phosphorylation with ATP[123]; however, the enzyme now exhibits incorporation of radioactive phosphate[123-127], which is not found with the enzyme that has not been treated with ouabain[105]. All the criteria available at present indicate that the phosphorylation with inorganic phosphate yields the same enzyme phosphate as the phosphorylation with ATP (step IV)[124,126,127]. To explain these observations, it is assumed that the enzyme is converted into a ouabain-enzyme complex (steps VI and VII).

3.3. Chemical Nature of the Phosphorylated Intermediate

The intermediate obtained from the ouabain-treated ATPase by phosphorylation with [^{32}P]-phosphate and the intermediate obtained from the untreated enzyme by Na^+-dependent phosphorylation with terminally labeled [^{32}P]-ATP exhibit chemically identical behavior according to all the investigation methods known at present[124,126,127]. Both products migrate at the same rate on electrophoresis; they are rapidly hydrolyzed in alkaline media and in the presence of molybdate and Hg^{2+}[106,124-128]. It has been shown that the phosphoryl-

ated intermediates are not phosphatidic acids or protein-bound serylphosphate[128-130].

Evidence in favor of an acylphosphate as the intermediate of the $(Na^+ + K^+)$-activated ATPase is the fact that the enzyme-bound phosphate is liberated as inorganic phosphate on incubation with the purified acylphosphatase or hydroxylamine [eq. (3)][106, 107, 128]:

$$E{-}COPO_3H_2 + NH_2OH \longrightarrow E{-}CONHOH + H_3PO_4 \quad (3)$$

Kahlenberg et al. assume that the phosphate acceptor group in the Na^+-dependent phosphorylation with ATP is the γ-carboxyl group of a glutamate residue[131, 132]. After incubation of the acid-denatured phosphorylated enzyme with ^3H-labeled *N*-propylhydroxylamine, the authors were able to isolate a ^3H-labeled peptide, which gave a homogeneous radioactive product on digestion with pronase and electrophoretic and chromatographic separation. In five out of seven electrophoretic and chromatographic systems, this radioactive product behaved in the same way as authentic glutamyl-*N*-propylhydroxamate.

With the native enzyme, hydroxylamine has no effect on the $(Na^+ + K^+)$-activated hydrolysis of ATP[133, 134]. This is in conflict with the assumption of an acylphosphate intermediate. Since the phosphate acceptor group is irreversibly blocked by conversion of an acylphosphate into the hydroxamic acid [eq. (3)], at least partial inactivation should be expected. However, *Chignell* and *Titus*[135] were able to show that the hydroxylamine does not reach the active center. ATP and Na^+, which must always be present in the phosphorylation reaction [eq. (1)] probably prevent the NH_2OH from approaching the acylphosphate in the active center. A protective action of ATP, Na^+, and K^+ has been detected in inactivation experiments with dicyclohexylcarbodiimide, a substance that reacts with carboxyl groups[136].

Doubt has recently been cast on the intermediate formation of an acylphosphate on thermodynamic grounds. The formation of an acylphosphate from inorganic phosphate is difficult to imagine, unless the inorganic phosphate breaks an energy-rich bond that is formed by the preincubation with ouabain.

3.4. Relationship between $(Na^+ + K^+)$-Activated ATPase and K^+-Activated Phosphatase

The membrane fractions with $(Na^+ + K^+)$-activated ATPase regularly contain a phosphatase that can be activated with potassium ions. The enzyme is also inhibited by ouabain[136-152]. The substrates of the enzyme are carbamylphosphate, acetylphosphate, and *p*-nitrophenylphosphate[140]; K^+ can be replaced by other alkali metal ions and by ammonium ions[137, 139]. Sodium ions and nucleoside diphosphates and triphosphates inhibit the enzyme activity[137, 138, 148]. Incubation of the membranes with [^{32}P]-acetylphosphate leads to the formation of a phosphorylated enzyme, which has the same properties as the phosphorylated enzyme obtained in the Na^+-dependent phosphorylation with [^{32}P]-ATP[138, 143]. All these properties and the detection of the increase in the specific activity of the K^+-activated phosphatase together with the $(Na^+ + K^+)$-activated ATPase indicate that the K^+-activated phosphatase catalyzes the K^+-dependent reaction step of the $(Na^+ + K^+)$-activated ATPase [eq. (2)][137, 140].

3.5. Kinetic Studies on the Process of Cation Activation

The investigations on the behavior of the phosphorylated intermediate toward ADP and K^+ at various Mg^{2+} concentrations suggest that the $(Na^+ + K^+)$-activated ATPase undergoes a change in conformation during the transport of cations. Further evidence in favor of this assumption can be obtained from kinetic studies on the activation of the enzyme by Na^+ and K^+. Thus *Squires*[153] and *Robinson*[154, 155] found a homotropic cooperative effect of both cations on the enzyme. Variation of the concentrations of both cations leads to changes in the cooperativity of the enzyme (compare *n* values in Table) and its affinity for the other cation (compare $K_{0.5}$ values in Table). The affinity of the enzyme for ATP is also controlled by the Na^+ and K^+ concentrations. With increasing K^+ concentration, the affinity of the enzyme for ATP decreases. A change in the ATP concentration, on the other hand, influences the concentrations of both cations that are required for half-maximal activation of the enzyme[154].

Table. Variation of the kinetic parameters of the $(Na^+ + K^+)$-activated ATPase for Na^+ and for K^+ with the concentration of the other cation (after *Robinson* [155]).
n = Hill coefficient, $K_{0.5}$ = activation constant of cation, rel. V_{max} = maximal velocity of ATP hydrolysis.

Activator	NaCl (mmole/l)	KCl (mmole/l)	*n*	$K_{0.5}$ (mmole/l)	V_{max}
NaCl	—	0.8	1.57±0.05	1.7±0.3	0.69±0.02
	—	2.0	1.35±0.06	2.8±0.6	0.91±0.04
	—	10.0	1.17±0.03	5.0±0.7	1.03±0.02
	—	30.0	1.22±0.08	6.3±1.3	1.08±0.05
KCl	3	—	0.75±0.06	0.18±0.04	0.53±0.04
	5	—	1.08±0.11	0.15±0.01	0.63±0.02
	10	—	1.28±0.09	0.19±0.03	0.74±0.05
	90	—	1.41±0.04	0.75±0.11	1.03±0.02

The change in the activation constants $K_{0.5}$, *i.e.* the concentrations of the cations that are required for half-maximal activation, was evident even in the first description of the enzyme by *Skou*[86] (see Fig. 2). *Skou* assumed that this displacement of $K_{0.5}$ values was due to competition of the K^+ for the Na^+ binding sites and of the Na^+ for the K^+ binding sites, a view that was also shared by other authors[50, 86, 97, 156]. Kinetic studies yielded no definite information about the number of binding sites for Na^+ and K^+. *Ahmed et al.*[157] postulated two Na^+ binding sites per K^+ binding site, whereas *Robinson*[155] assumes several binding sites for Na^+ and K^+, which can be occupied simultaneously or successively.

3.6. Studies for the Detection of Na^+ and K^+ Binding Sites

The direct detection of Na^+ and K^+ binding sites on the enzyme has not yet been possible because of the impurity

of the enzyme preparations. An ATP-dependent binding of Na^+ on rat brain microsomes has been described by *Järnefelt* and *von Stedingk*[158]. In their studies, half-maximal saturation of the microsomes by Na^+ was found at a concentration of 0.1 mole/l. However, $(Na^+ + K^+)$-activated ATPase is activated half-maximally by Na^+ at much lower concentrations Fig. 2[86, 155]. From this comparison it is evident that the Na^+ binding site found by *Järnefelt* and *von Stedingk* is not involved in the active Na^+ transport. In addition, *Ahmed* and *Judah*[159] could show that the ability of the microsomes to bind Na^+ is increased to a much greater extent by EDTA than by ATP. The authors therefore concluded that Mg^{2+} completes with Na^+ for the acceptor site. Nonspecific binding of Na^+ to the cell membrane is also indicated by the fact that equal quantities of H^+/mg of protein are released on addition of NaCl, KCl, or LiCl in a concentration of 0.1 mole/l to microsomes.

The phosphorylation experiments with terminally labeled [^{32}P]-ATP[96, 98, 104–113] could give the impression that ATP is necessary for the cation-specificity of the enzyme. On the basis of inhibition experiments with diisopropyl fluorophosphate[160], *N*-ethylmaleimide (NEM)[161], and $BeCl_2$[162], however, it must be assumed that Na^+ and K^+ react specifically with the enzyme even in the absence of ATP[162]. Thus in the absence of ATP, sodium ions protect the $(Na^+ + K^+)$-activated ATPase against inactivation by $BeCl_2$, while K^+ strengthens the inactivation[162, 163]. The protective and inactivating effects of the cations occur at concentrations that lie in the physiological range.

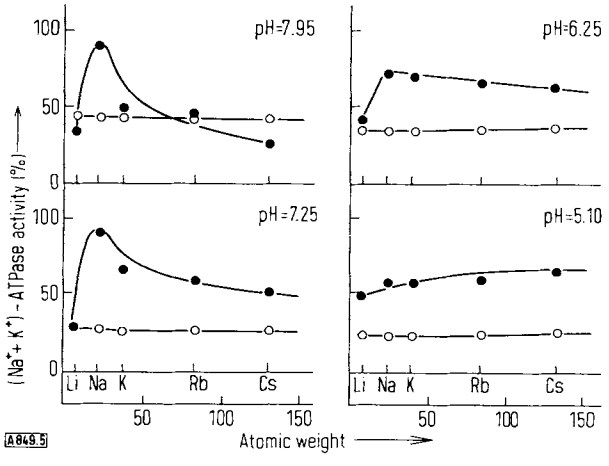


Fig. 5. Protective action of alkali metal ions against the inactivation of $(Na^+ + K^+)$-activated ATPase by dicyclohexylcarbodiimide (DCCD) as a function of the pH value (after *Schoner* [165]). Ordinate: ATPase activity after incubation for 6 min with DCCD with reference to the control without DCCD (in percent). ● = cation concentration 60 mmole/l; ○ = control without cation.

In our own investigations, we observed a pH-dependent change in the protective effect of alkali metal ions against the inactivation of the $(Na^+ + K^+)$-activated ATPase by dicyclohexylcarbodiimide (Fig. 5)[164, 165]. This result suggests that the cation specificity changes with changing dissociation of an acidic group of the enzyme. This is in agreement with the observed displacement of the pH optimum of the $(Na^+ + K^+)$-activated ATPase with the Na^+/K^+ ratio in the test medium[165–167].

3.7. Mode of Action of Cardiac Glycosides

Cardiac glycosides specifically inhibit the active transport of Na^+ and K^+ and the $(Na^+ + K^+)$-activated ATPase[66, 168]. Further information about the processes involved in the transport of Na^+ and K^+ should therefore be obtainable by the investigation of the mode of action of these inhibitors. The inhibitory action of the cardiac glycoside ouabain is a time- and temperature-dependent process. The onset of action is strongly accelerated by the simultaneous presence of Mg^{2+}, Na^+, and ATP[125]. This suggests that ouabain reacts with the phosphorylated enzyme[169, 170]. In agreement with this assumption, it has been shown that the simultaneous presence of Mg^{2+}, Na^+, and ATP is necessary for the binding of ^{3}H-labeled cardiac glycosides[125, 171, 172]. Ouabain reacts in stoichiometric quantities with the enzyme (one molecule of ouabain per two phosphorylation sites)[125, 173].

The phosphorylated enzyme can be obtained not only under physiological conditions (step I in Fig. 4) but also by incubation of the enzyme with ouabain, inorganic phosphate, and Mg^{2+} (steps IV, VII, and VI in Fig. 4)[125–127]. The phosphorylated enzyme obtained in this way also binds more [^{3}H]-ouabain than the native enzyme[172].

The quantity of [^{3}H]-ouabain bound to the enzyme under these last conditions decreases strongly in the presence of Na^+[172], whereas an Na^+-dependent increase in the uptake of [^{3}H]-ouabain is observed in the presence of Mg^{2+} and ATP[125, 171, 172]. The *Na^+-dependent increase* in the binding of ouabain to the $(Na^+ + K^+)$-activated ATPase in the presence of Mg^{2+} + ATP and the *Na^+-dependent inhibition* of the binding of ouabain in the presence of Mg^{2+} + inorganic phosphate (P_i) show that "the conformational state of the enzyme is probably of primary significance in glycoside binding[173]".

According to *Tobin* and *Sen*[172], the equilibrium between the two assumed conformations of ATPase, *i.e.* E_1 and E_2, is displaced in favor of E_2 by Mg^{2+} and P_i (step IV in Fig. 4). In this form, which is equivalent to E_2-P, ouabain can be bound to the enzyme. Ouabain holds the enzyme in the E_2 conformation. The affinity of Na^+ for the enzyme is also lower in this conformation. The equilibrium between E_1 and E_2 is displaced in favor of E_1 in the presence of Mg^{2+} and P_i if Na^+ is present in higher concentrations. Under these conditions, ouabain cannot be bound. E_1 should thus be sensitive to Na^+ in its phosphorylated and in its unphosphorylated forms.

This assumption is supported by the detection of a specific protective action of Na^+ against the inactivation of the $(Na^+ + K^+)$-activated ATPase by $BeCl_2$[162, 163] and the antagonistic action of K^+ on the non-phosphorylated enzyme.

3.8. Properties of the Enzyme-Bound Cardiac Glycoside

The enzyme-bound radioactive steroid does not exchange its radioactivity with unlabeled cardiac glycosides. However, it is released from the enzyme at higher temperatures and in acidic media below pH 5, and can be extracted with

methanol[125, 174]. On the basis of the extractability and the observation that the time required for the inhibitory effect of the steroids to appear is inversely proportional to the number of hydroxyl groups and of sugar substituents, *Albers et al.*[125], in agreement with assumptions made by *Portius* and *Repke*[170], concluded that the cardiac glycosides enter into hydrophobic interactions with hydrophobic regions of the enzyme. However, this assumption is opposed by investigations carried out by *Yoda* and *Hokin*[175], which showed that the inhibitory action of the aglycones of the cardenolides is more readily reversible than that of the glycosides.

4. Outlook

The detection of Na^+-specific protective effects against inactivating agents in the absence of ATP[162–165] indicates that cation-specific acceptor groups are present on the enzyme. The phosphorylated intermediate does not therefore appear to be involved in the occurrence of the cation specificity, but probably takes part in the transport of the cations through the cell membrane. This process is probably associated with a change in the conformation of the enzyme[114, 115, 123, 124, 171–173]. It is uncertain whether carriers are involved in the transport of the cations. It is to be hoped that the answer to this question will be provided by further investigations on the mode of action of the $(Na^+ + K^+)$-activated ATPase.

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Ternary Fission[**]

By Reinhard Brandt[*]

In this review paper, ternary fission is defined as the break-up of heavy nuclei into three fragments of approximately equal mass. This relatively new type of nuclear decay has been investigated intensively during the last decade. Muga has studied ternary fission induced by thermal neutrons in uranium. The results of his experiments are discussed in detail. Ternary fission can definitely be observed and studied in the interaction of heavy target elements with 39 MeV alpha particles, 20 GeV protons, and 300—400 MeV argon ions. The ratio of binary-to-binary fission for uranium is approximately 10^{-4}: 100 in the interaction of 39 MeV alpha particles, approximately 0.1 : 100 for 20 GeV protons, and 3 : 100 for 400 MeV argon ions. A theoretical model for the interpretation of ternary fission, the "cascade model", is described. The paper concludes with a discussion of the possible connection of ternary fission with the production and decay of still undiscovered superheavy elements ($Z = 114$).

1. Introduction

Binary fission was discovered in 1938. The "liquid drop" model of the nucleus was used from the beginning to interpret this new phenomenon. Using this model *Present*[1] pointed out as early as 1941, that the disintegration of nuclei into three particles of equal mass should be possible. Such a nuclear disintegration will be defined in this paper as ternary fission; fission yielding two heavy particles and one light particle (usually an alpha particle) will not be dealt with here. Later, *Swiatecki*[2] studied the application of the liquid drop model for the interpretation of fission. In this model it is assumed that the nucleus is an ideal, electrically charged, spherical liquid drop. Such a liquid drop has a surface tension of $E_s^{(o)}$ and a Coulomb energy of $E_c^{(o)}$. It is common practice to express the ability of such a drop for fission in terms of a *fissionability parameter*, X, defined as follows:

$$X = \frac{E_c^{(o)}}{2 \cdot E_s^{(o)}} \tag{1}$$

It is possible to calculate $E_c^{(o)}$ and $E_s^{(o)}$ for nuclei carrying a nuclear charge Z and mass A. When rather simple semi-empirical parameters are chosen, X is[3]:

$$X = \frac{Z^2/A}{(Z^2/A)_{crit.}} \qquad (Z^2/A)_{crit.} = 50.1 \tag{2}$$

The decay energy for fission of a nucleus into n equally sized fragments, and its dependence on the fissionability parameter X, has been calculated by *Swiatecki*[2] for several values of n. The results, which are shown in Figure 1, allow the following conclusions to be drawn:

1. Fission of light nuclei is only exothermic when $Z^2/A > 17$. Binary fission is energetically more favorable than ternary fission.

2. The range of $30.5 < Z^2/A < 43.3$ covers the elements from $_{83}$Bi up to $_{100}$Fm. These elements are the targets most commonly used in fission studies. For these nuclei, the decay energy for ternary fission is larger than for binary fission. Based on this simple consideration, many attempts were made to observe ternary fission. All of them were without success until 1966.

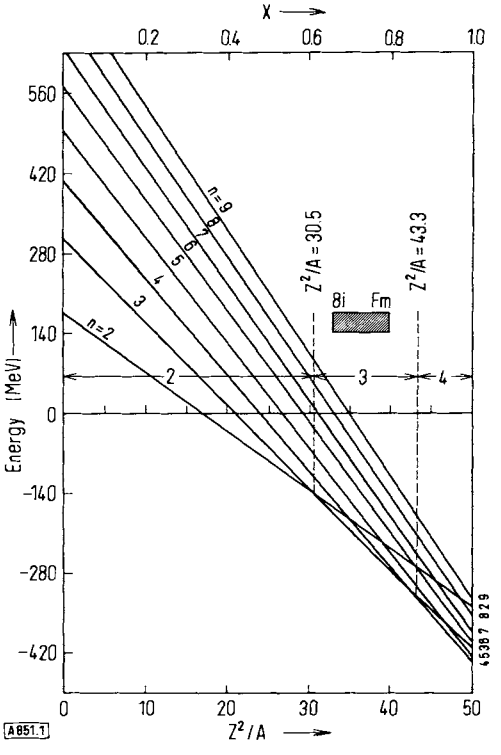


Fig. 1. Decay energy of an ideal, electrically charged liquid drop as a function of the fissionability parameter X and of the value Z^2/A. The parameter n gives the number of equally sized fission fragments obtained in the decay process [2]. Fission into two fragments is energetically favored for $Z^2/A < 30.5$, ternary fission is energetically most favorable for $30.5 < Z^2/A < 43.3$. Fission into four fragments gives the largest amount of kinetic energy for $Z^2/A > 43.3$.

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[**] A condensed version of an invited paper given at the "Heavy Ion Seminar on Nuclear Fission and Superheavy Elements", The Technical University, Darmstadt, 1970. The seminar was arranged by the "Gesellschaft für Schwerionenforschung, GSI", Darmstadt.

3. Stable nuclei are unknown for $Z^2/A > 43.3$. However, for undiscovered elements, multiple fission should become more and more probable.

4. The biggest possible value of Z^2/A for the target system should be chosen when investigating ternary fission.

Experiments for the study of ternary fission will be described in the following section. These investigations are interesting in two respects: Firstly, this new type of nuclear decay was predicted theoretically. Secondly, there is reason to believe that the production and decay of possibly stable elements around $Z = 114$ might be connected with ternary fission. This rather speculative working hypothesis will be discussed at the very end of this review paper.

2. Experimental Investigation of Ternary Fission

2.1. The Fission of Uranium and Plutonium with Thermal Neutrons

2.1.1. Counter experiments by *Muga et al.*

For several years, *Muga* and his co-workers have been investigating ternary fission of uranium and plutonium induced by thermal neutrons[4-8]. They use three fission-fragment detectors, employed in the coincidence mode. Figure 2 shows the geometrical arrangement of the target (U or Pu on a thin backing) and the three fission-fragment detectors in a vacuum chamber. This chamber is exposed to the thermal neutrons of a reactor. Further, since it is assumed that the three fission fragments separate at angles of approximately 120°, the detectors are arranged correspondingly. The three fission fragments reach the detector

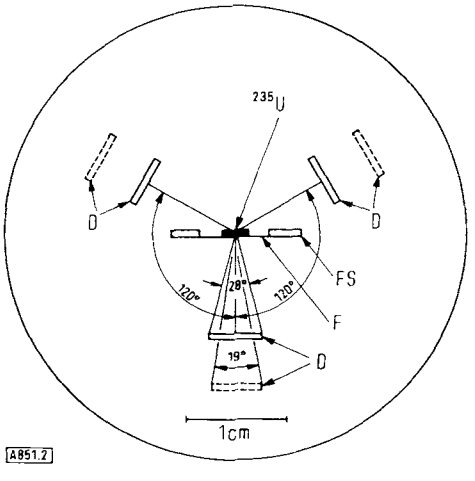


Fig. 2. Experimental arrangement for ternary fission studies of ^{235}U with thermal neutrons. D: fission fragment detectors, F: foil to hold the ^{235}U-target, FS: target holder [5].

within a time interval of 20 ns. Their kinetic energy E is then measured and registered electronically. Further details of the electronic apparatus and the method of data handling are not given here, but may be found in References [4]—[8].

The determination of the ratio of ternary fission $\sigma(T)$ to binary fission $\sigma(B)$ is an essential result of these studies[*]:

$\sigma(T):\sigma(B) \approx 10^{-4}:100$
Reaction: $^{239,241}Pu + n_{th} \longrightarrow$ ternary fission (3)
Method: counter experiment

Proof of the existence of ternary fission (TF) is obtained in an indirect rather than in a direct manner. Figure 3 shows, for example, the distribution of the lightest fragments in the ternary fission of ^{239}Pu and ^{241}Pu induced by thermal neutrons. The two distributions differ significantly from each other. For *Muga*, this statistically significant difference was proof that he had observed ternary fission and not a scattering phenomena or an electronic malfunction. *Muga* can not explain the reason for this difference; however, this is irrelevent here.

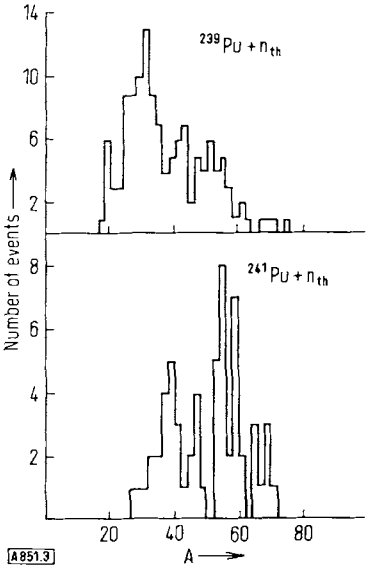


Fig. 3. Mass-distribution for the lightest fragment in ternary fission of ^{239}Pu and ^{241}Pu with thermal neutrons [8].

The most surprising result, which can be drawn from Figure 3, is the existence of fragments in the mass range $25 < A < 70$. Due to the experimental technique employed, it is not known whether these light fragments are beta-stable or not, that is, whether or not they can be detected by radiochemical methods.

Muga's experimental results have not been generally accepted. Recently, *Steinberg*[9] *et al.* showed that *Muga*'s results can be explained to a large extent as scattering phenomena. It is the opinion of the author of this review, that this issue has not been completely settled, as experiments using advanced time-of-flight techniques for mass determinations, have not been conducted and published.

2.1.2. Radiochemical Experiments

The mass distribution of the lightest fission fragment in ternary fission, as shown in Figure 3, has induced a number

[*] The cross-section σ is a quantitative measure for nuclear reaction probabilities. Its unit is 1 barn ($1\ b = 10^{-24}\ m^2$). Further details may be found in many textbooks on nuclear chemistry, for example, *M. Lefort*: "Nuclear Chemistry", Van Nostrand Company, New York.

of radiochemists to search for radioactive products in the mass-range of $20 < A < 60$[10–12]. These investigations have been necessarily restricted to sufficiently long-lived radioactive nuclides such as ^{28}Mg, ^{38}S, ^{37}Ar, ^{39}Ar, ^{41}Ar, ^{42}Ar, ^{48}Sc, ^{51}Cr, ^{54}Mn, ^{56}Co, ^{57}Co, ^{58}Co, ^{60}Co, and ^{59}Fe. However, as no such radioactive products could be found, one can give a lower limit for ternary fission:

$\sigma(T):\sigma(B) \leq (10^{-6}—10^{-8}):100$
Reaction: $^{235}U + n_{th} \longrightarrow$ ternary fission (4)
Method: radiochemical experiment

As already mentioned, this negative result does not necessarily exclude the correctness of *Muga*'s work[4–8], since non-radioactive light fission fragments are also observed with the latter technique.

2.2. Experiments at Medium Bombarding Energies (10—50 MeV)

Initial research in this field has been reviewed elsewhere by *Hyde*[3] and therefore shall not be repeated here. Likewise, the experiments carried out by *Benisz et al.*[13] and *Medveczky et al.*[14] shall be mentioned only briefly here.

A particularly elegant proof for the existence of ternary fission was given by *Iyer* and *Cobble*[15, 16], who irradiated uranium with alpha particles and determined the cross-section for light fragments such as ^{24}Na, ^{28}Mg, and ^{38}S

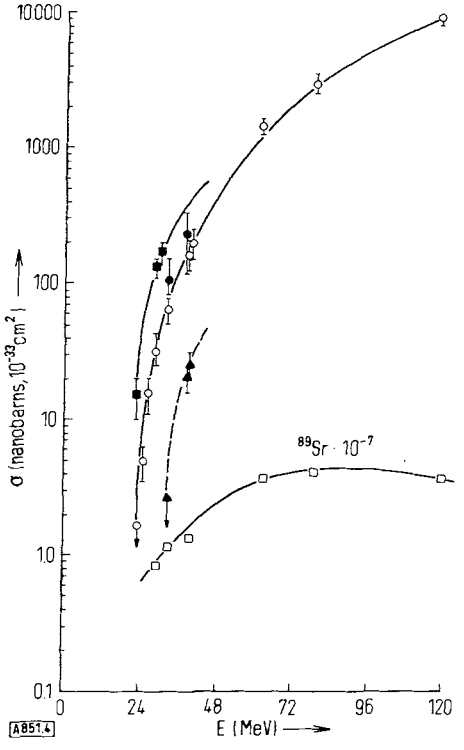


Fig. 4. Excitation function of some radioactive products produced by ^{3}He-induced fission of ^{238}U [16]. σ: cross-section, E: bombarding energy.
■: ^{238}U (^{3}He, f$_t$) ^{28}Mg
●: ^{238}U (^{4}He, f$_t$) ^{24}Na
○: ^{238}U (^{4}He, f$_t$) ^{28}Mg
▲: ^{238}U (^{4}He, f$_t$) ^{38}S
□: ^{238}U (^{4}He, f$_b$) ^{89}Sr

by radiochemical methods. The excitation function[*] for the production of these nuclides is shown in Figure 4. The measured cross-sections were extremely small, being in the order of $\sigma \approx 10^{-32}$ cm^2. The nuclides searched for had to be separated from a 10^7-fold excess of common binary

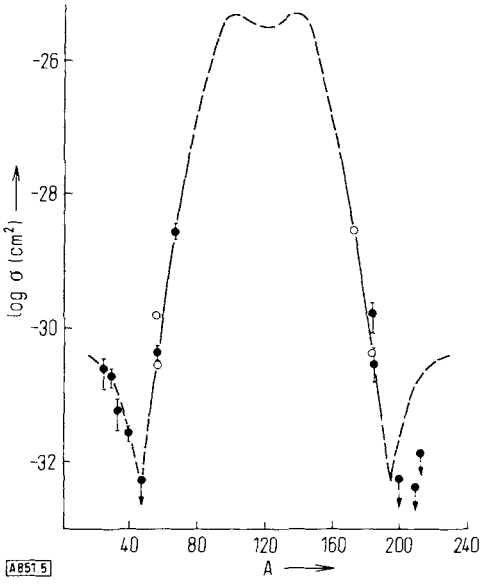


Fig. 5. Mass yield curve for fission of ^{238}U induced by 39 MeV ^{4}He [16]. Closed points are directly measured, open points are reflected.

fission products. The isolated samples showed counting rates of 1 to 100 counts-per-minute. However, the identity of an isolated chemical isotope was assured by the chemical separation technique and by the determination of the radioactive half-life. In order to exclude the possibility that light fragments were not created in a very asymmetric binary fission process, *Iyer* and *Cobble* searched for the complimentary heavy fragment in the mass-range $A \approx 190$. Such heavy fission fragments could not, however, be detected. The measured mass-yield curve is shown in Figure 5. The very light fragments with $20 < A < 60$ were formed in a considerably higher yield than very heavy fragments with $A \approx 190$. This shows conclusively that light fragments such as ^{28}Mg are formed by a ternary fission process when ^{238}U is bombarded with 39 MeV alpha-particles.

2.3. Ternary Fission Induced by 20 GeV Protons

Modern high-energy accelerators, such as at CERN, Geneva, provide proton beams of considerable energy, usually of about 28 GeV (1 GeV = 10^9 eV). In the interaction of high energy protons with complex heavy nuclei, such as ^{238}U, a variety of nuclear reactions are observed. These reactions can be understood only partially on the basis of present theoretical models[3, 17]. Nevertheless, nuclear reactions yielding two or three "heavy" fragments are also classified as binary or ternary fission. The definition of "heavy" depends again on the kind of experiment to be carried out.

[*] The "excitation function" is defined as the dependence of the cross-section σ of a particular nuclear reaction product on the energy of the bombarding particle.

The dependence of the total fission cross-section of heavy elements on the proton energy has been studied using the mica-sandwich technique. Mica is a widely used detector for fission fragments having a mass $A \geq 30$. The fission fragment tracks are etched with hydrofluoric acid and can be observed directly with an optical microscope (see Fig. 6)[18, 19]. High energy protons can not be detected with mica[20]. Further experimental details are described in References [22] to [26].

The tracks made by the fission fragments are clearly seen under an optical microscope. One can observe correlated pairs of tracks (B), obviously originating from binary fission. The point of origin of such correlated pairs of tracks is not visible, since the decaying uranium atom (target) is placed between the mica plates (sandwiched).

The cross-section for binary fission $\sigma(B)$ is determined from the number of pairs of correlated tracks in the sandwich[21, 23, 24]. Sometimes, single, uncorrelated tracks (S) can be seen, as is also shown in Figure 6. Their origin is not completely clear; however, it has been shown that they originate to a large extent from binary fission events with one fragment being absorbed within the target and thus not yielding an etchable track[21, 22, 25].

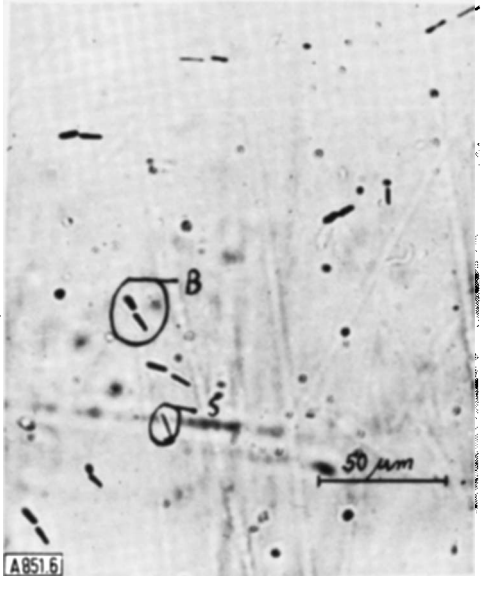


Fig. 6. Photomicrography of typical examples of correlated pairs of fission fragments (B) as well as single tracks (S). The two inner surfaces of the mica sandwich are simultaneously in focus. Reaction: $^{238}U + 20$ GeV protons.

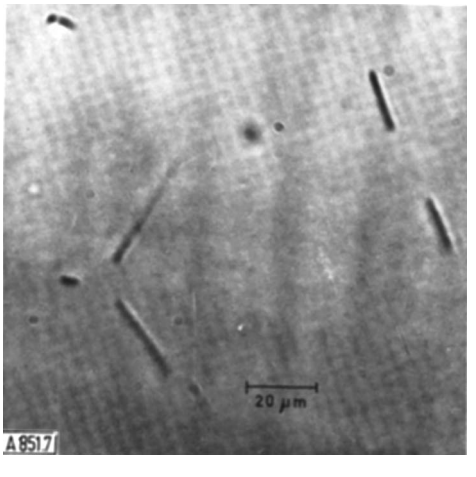


Fig. 7. Photomicrography of a possible example of ternary fission in the reaction $^{238}U + 20$ GeV protons.

In relatively few instances one can observe three correlated tracks (T) as shown in Figure 7. Such an event can have a twofold origin: either it is an accidental overlap of a binary track (B) and a single track (S), or it is a genuine ternary fission. The largest angle α between two tracks in the plane of observation is measured for all ternary events in order to distinguish between the two alternative interpretations. The observed distribution of α is shown in Figure 8. Quite often the angle α is approximately 140°. The corresponding distribution of angles for binary fission is also measured; here practically all angles are approximately 180°[26]. One can now calculate the expected distribution of the largest angle α for an accidental overlap of binary (B) and single (S) tracks. This is also shown in Figure 8.

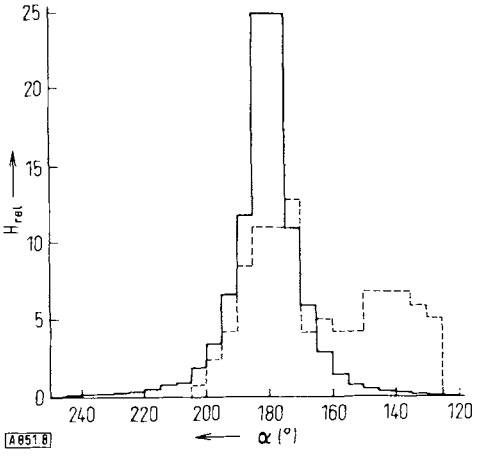


Fig. 8. Distribution of the largest angle α in the mica plane for all possible examples of ternary fission. H_{rel} = relative probability; – – –: observed distribution, ——: expected distribution for *no* ternary fission. $\chi^2 = 585$ ($\gamma = 2$), $P(\chi^2) \ll 1\,‰$.

The two distributions shown in Figure 8 differ considerably, and are statistically significant (χ^2-test). This is proof for the observation of ternary fission in the interaction of uranium with 20 GeV protons, provided that the possibility of this being a scattering phenomena is excluded. This can be done by comparing the ratio of $\sigma(T):\sigma(B)$ as a function of the irradiation energy, as shown in Table 1. An increase in the ratio of $\sigma(T):\sigma(B)$ with irradiation energy demonstrates that this is not a scattering of fission fragments giving rise to false ternary fission events (Fig. 7). Additional independent methods of proving the existence of ternary fission have also been published[26, 27]. In all, about 200 events of the kind shown in Fig. 7 have been observed.

Table 1. Dependence of $\sigma(T):\sigma(B)$ for uranium on the bombarding energy using the mica sandwich technique [27].

Energy and particle	$\sigma(T):\sigma(B)$	$\sigma(T)$ (mb)
thermal neutrons	$\leq 1.3 \cdot 10^{-2}:100$	—
600-MeV-protons	$(0.2 \pm 0.1):100$	2.0 ± 1.5
18-GeV-protons	$(0.18 \pm 0.06):100$	1.5 ± 1.1
23-GeV-protons	$(0.48 \pm 0.16):100$	3.5 ± 1.2

Further characteristics of ternary fission are difficult to determine using the sandwich technique. The measurement of the direction of an etched track in space is rather inaccurate[27]. (The direction of a track in space can be determined about as accurately as can that of the direction of a pointing finger.) With these reservations in mind, one

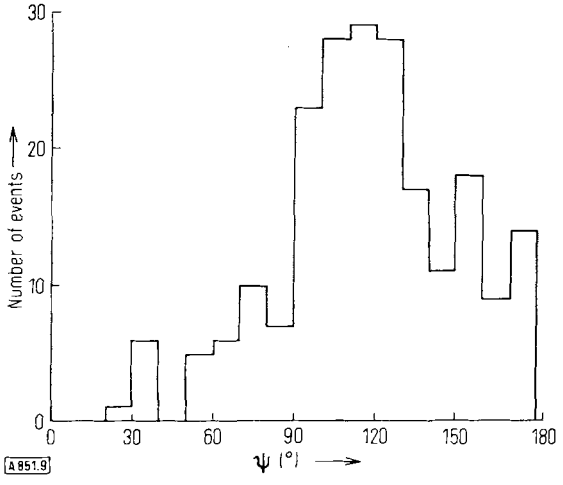


Fig. 9. Distribution of angles between fission fragments in ternary fission of ^{238}U with 20 GeV protons (simplified figure after Ref. [27]). ψ = angle between fission fragments.

can determine the angle in space between tracks of ternary fission events (see Fig. 9)[27]. It is usually about 120°, indicating that ternary fission is a planar and symmetrical decay process in the laboratory system. However, it must be pointed out that the mica sandwich technique does not allow the evaluation of mass-distributions in ternary fission.

Two other groups of research-workers have also observed ternary fission under similar conditions. *Hudis* and *Katcoff*[23] determined the excitation function of ternary fission for uranium-, bismuth-, and gold-targets in the GeV region. *Debeauvais et al.*[28,29] carried out similar studies, using a more sensitive detector, called "Macrophol", which registered all particles with mass $A \geq 14$.

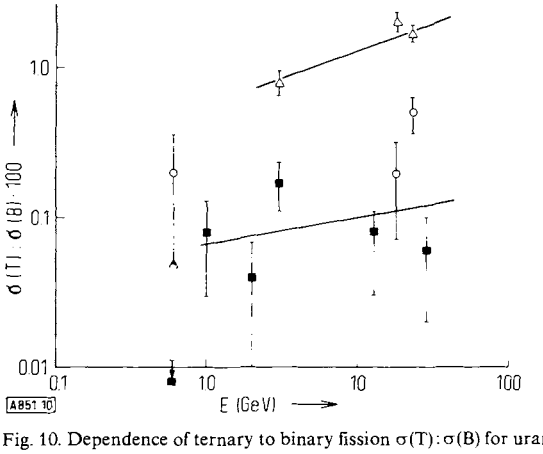


Fig. 10. Dependence of ternary to binary fission $\sigma(T):\sigma(B)$ for uranium on the proton bombarding energy.
△: Results obtained with macrophol detectors ($A \geq 14$) at Strasbourg [29].
○: Results obtained with mica detectors ($A \geq 30$) at Geneva [27].
■: Results obtained with mica detectors ($A \geq 30$) at Brookhaven [23].

Obviously, a considerably greater number of ternary fissions is observed with this more sensitive detector (the ratio $\sigma(T):\sigma(B) \approx 1:100$). The excitation function of ternary fission for uranium obtained by different techniques is summarized in Figure 10[23,27,29].

Finally, it should be mentioned that ternary fission in the reaction U + 20 GeV protons was observed by a further independent experimental technique. This technique,

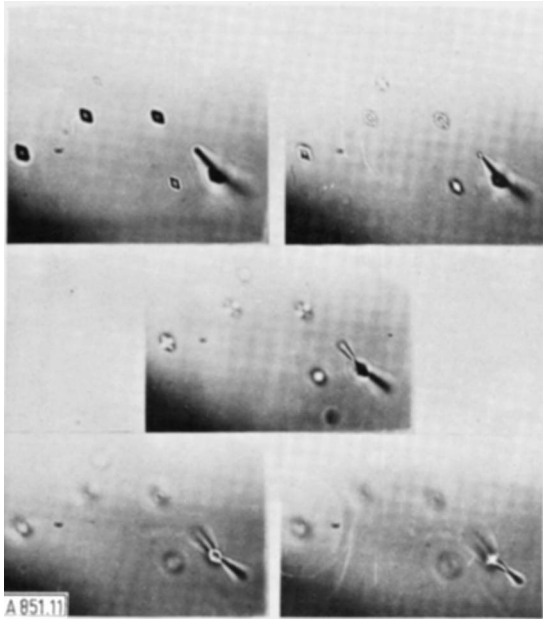


Fig. 11. Hole detector in mica, after *Starke*. In this sequence of photomicrographs only the focal plane of observation is subsequently lowered from picture to picture; thus a binary fission event in one hole can be observed. Nuclear reaction: ^{238}U + 20 GeV protons [30].

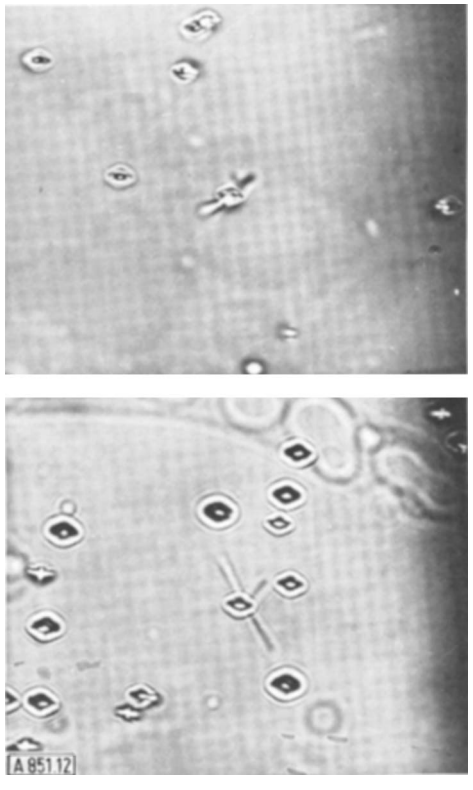


Fig. 12. Two possible examples of ternary fission in the reaction of ^{238}U with 20 GeV protons, as observed in the hole detector, after *Starke*.

known as the "hole-detector" method, was introduced by *Starke*[30]. Fine holes are produced in mica by etching fission fragment tracks on the surface and are partially filled with uranium. The mica is then irradiated with 20 GeV protons and then re-etched with hydrofluoric acid. A sequence of photomicrographs of a binary fission event in such a hole is shown in Figure 11. (Only the focal plane was changed for each picture.) Two possible examples of ternary fission observed in these holes are shown in Figure 12. However, the potentialities of this method have not as yet been worked out.

2.4. Ternary Fission Induced by Heavy Ions

Heavy ions such as neon or argon can be accelerated in "heavy ion accelerators" to such energies as to render them capable of inducing nuclear reactions. These heavy ions usually induce nuclear fission in heavy target elements. In this case it can be assumed that target nuclei and projectile fuse together and form a so-called "compound nucleus". This compound nucleus has a well-defined and rather high Z^2/A, as well as a well-determined excitation energy E_{ex}. (This is in contrast with high-energy proton induced reactions, where Z^2/A and E_{ex} for the fissioning nuclei are practically unknown.) As mentioned in the introduction, according to *Swiatecki*'s arguments it is plausible to search for and investigate ternary fission with heavy ions. One theoretical model for the interpretation of ternary fission induced by heavy ions does exist. This is discussed further on in Section 3.1. Unfortunately, there have been only a limited number of investigations in this field; most of these have been carried out with the heavy ion accelerators at Berkeley (USA) and at Dubna (USSR).

These experiments will be described according to the experimental method used for investigation. Hence, the work of *Fleischer*, *Price*, *Walker*, and *Hubbard*[31] will unfortunately be mentioned last, despite the fact that they were the first to prove the existence of ternary fission in the interaction of 414 MeV-Ar with Th in $ThSiO_4$-crystals. They still hold the "world record" for having found the largest ratio for $\sigma(T):\sigma(B)=(3.3\pm0.3):100$.

2.4.1. Electronic Counter Experiments

In this field only two papers have been published[32, 33]. Figure 13 shows schematically the experimental arrangement for such electronic counter experiments. The arrangement is similar to that used by *Muga* (see Section 2.1.1); however, the fission fragment detectors are not placed in one plane, but rather are placed so as to account for the momentum of the incoming particle. The registration of ternary fission is restricted to events in which the angle between the fragments is $(120\pm8)°$ in the center-of-mass system. The energy of the fission fragments is measured with semiconductor detectors and is then registered electronically. The measured distribution of kinetic energies for two different reactions is shown in Figure 14. The mean total kinetic energy ("combined spectrum") increases with increasing Z of the projectile. Such a result can be predicted from knowledge of the general behavior of fission[3]. The ratio $\sigma(T):\sigma(B)$ can be obtained by measuring the ratio of threefold coincidences to the number of measured fission events (Table 2).

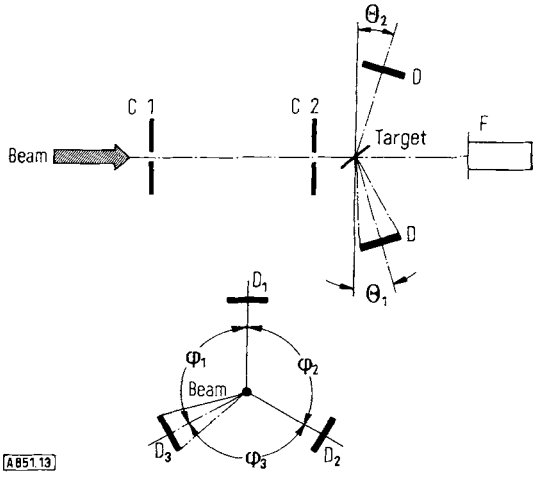


Fig. 13. The experimental arrangement for studying ternary fission induced by heavy ions [33]. C: collimator, D: fission fragment detector, F: Faraday cup.

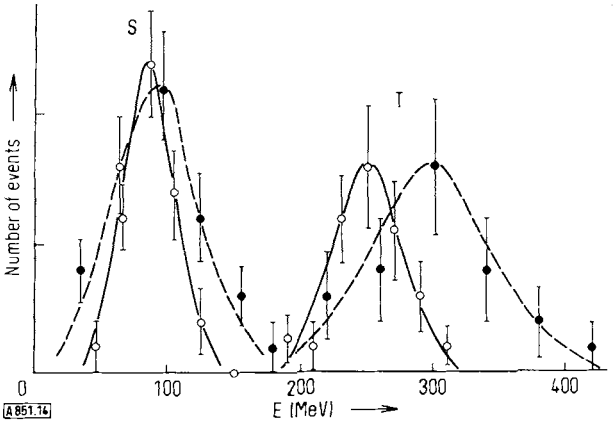


Fig. 14. Spectra of measured kinetic energies of fission fragments in ternary fission. S: spectrum of single fragments, T: spectrum of the sum of three fission fragment energies [32].
○: $^{238}U+185$ MeV Ne
●: $^{238}U+270$ MeV Ar

Two conclusions which may be drawn from Table 2 are:

1. The probability of ternary fission increases with increasing Z^2/A of the compound nuclei. However, one has to use rather heavy ions such as Ne or Ar in order to obtain rates of ternary fission high enough to be observed experimentally. In comparison to the values given in Table 2, *Muga*'s results appear to be rather high.

Table 2. The ratio of $\sigma(T):\sigma(B)$ for heavy ion induced ternary fission [32, 33].

Reaction	Heavy ion energy (MeV)	Z^2/A of compound nucleus	$\sigma(T):\sigma(B)$
$^{197}Au+^{22}Ne$	185	36	$7\times10^{-4}:100$
$^{238}U+^{22}Ne$	185	40	$(7.0\pm1.5)\times10^{-3}:100$
$^{209}Bi+^{40}Ar$	310	41	$(1.0\pm0.4)\times10^{-2}:100$
$^{238}U+^{40}Ar$	270	43.4	$(2\pm1)\times10^{-2}:100$
$^{238}U+^{40}Ar$	310	43.4	$(1.3\pm0.3)\times10^{-1}:100$

2. The probability of ternary fission increases drastically with the increasing excitation energy of the compound nucleus, as can be seen on the last two lines of Table 2.

In summary, the counting experiments establish the order of magnitude for the probability of ternary fission and yield information on the kinetic energy of the fission fragments. Little is known, however, about the angular distribution of fission fragments in ternary fission. This will be discussed in the next section.

2.4.2. Mica experiments

As was shown earlier (Section 2.3), the mica-sandwich technique yielded valuable information on ternary fission induced by 20 GeV protons. Unfortunately, the same technique did not work properly in 300 MeV Argon ion induced fission (see Reference [34]). Therefore, initial experiments were carried out using the so-called "2π-geometry" method. In this method uranium is evaporated onto a mica sheet, irradiated with argon ions, and then treated in such a way so as to reveal fission tracks[*]. Only those tracks which move forward in the laboratory system, and which are thus intercepted by the mica, are registered. When only one fission fragment moves forward, a single track (S) is seen, when two tracks move forward, a binary track (B) is seen. Sometimes three tracks move forward. An example of such an event has been photographed and is shown in Figure 15. This event is defined as ternary fission. The center of the fissioning nucleus is still outside

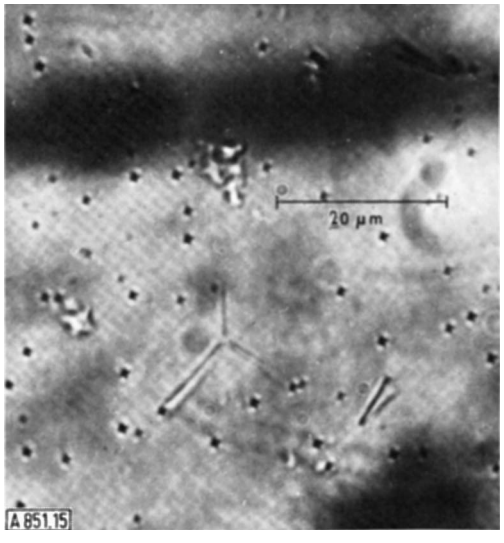


Fig. 15. Photomicrography of a ternary fission event of ^{238}U induced by 305 MeV ^{40}Ar and observed with 2π-geometry in mica [35].

the mica, but is restricted to a much smaller area than that seen in Figure 7. Therefore, an explicit proof of the existence of ternary fission is omitted in this part of the investigation.

It is now possible to count the binary (B) and ternary (T) fission events (as defined above) and to calculate the ratio $\sigma(T):\sigma(B)$ for this "2π-geometry" method. The results are shown in Figure 16.

[*] The proper treatment includes 6 hours' annealing of the argon-ion tracks at 430 °C, followed by etching with hydrofluoric acid [36].

1. The ratio $\sigma(T):\sigma(B)$ increases again with the increasing energy of the argon ion.

2. For a constant Ar-ion energy, the ratio $\sigma(T):\sigma(B)$ increases with the increasing Z^2/A of the compound nucleus.

3. The compound nucleus system has the same value for Z^2/A in the system $^{232}Th+Ar$ as in the system $^{238}U+Ar$. Therefore the ratio $\sigma(T):\sigma(B)$ is the same for both systems.

4. If the two values determined at 414 MeV argon energy using the 4π-geometry method (see Section 2.4.3) are compared with those values determined using the 2π-geometry method, it will be seen that the 2π-geometry method gives ratios of about a factor of 2 smaller.

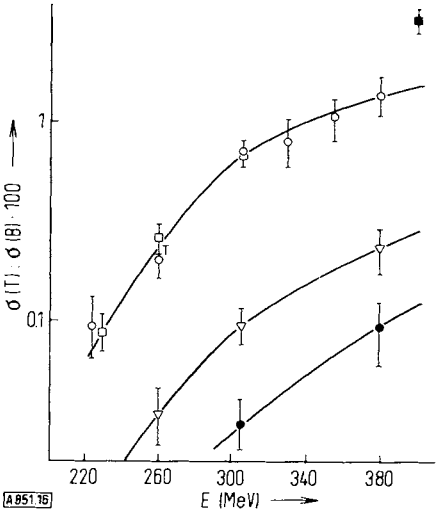


Fig. 16. Dependence of the ratio of ternary to binary fission $\sigma(T):\sigma(B)$ on the argon-ion energy, as measured with 2π- and 4π-geometry [35]. Details are given in the text. ○: U, □: Th; ▽: Bi, ●: Au with 2π-geometry; ■: Th; ▼: Pb with 4π-geometry.

The ratio for $\sigma(T):\sigma(B)$, as shown in Figure 16, is about a factor of ten larger when compared to the results shown in Table 2 (counter experiments). This is quite plausible, since the latter technique selects only events in which all angles in the center-of-mass system between the three fragments are $(120\pm8)°$. The "2π-geometry" method does not take these restrictions into account. Furthermore, a quantitative comparison between the two methods is difficult, since the registration threshholds also differ in each method.

The distribution of angles between fission tracks in ternary fission has been determined for a number of different compound nuclei and excitation energies[35]. It suffices, here, to show the angular distribution between the tracks in ternary fission for the reaction: U + 300 MeV Ar (Fig. 17). The angle with the highest probability is $\varepsilon_M \simeq 110°$; however, there is a wide distribution around this angle. The events with $\varepsilon < 100°$ and $\varepsilon > 120°$ are those which were not detected in the counting experiments described in Section 2.4.1. The distribution of the sum of three angles in ternary fission ($\varphi = \varepsilon_1 + \varepsilon_2 + \varepsilon_3$) is shown in Figure 17a. The most probable value is $\varphi_M = 320°$. This implies that the observed ternary fission events were rather "flat" events. However, this might also be due to the special detector arrangement used in the "2π-geometry" method. The values marked "model" were calculated theoretically on the assumption

that ^{238}U and ^{40}Ar form a compound nucleus and decay symmetrically into three fragments in a center-of-mass plane perpendicular to the direction of the beam. Furthermore, a kinetic energy of 100 MeV per fragment was used

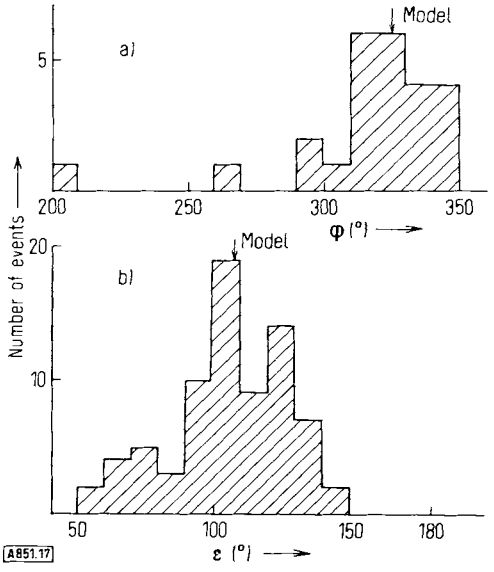


Fig. 17. a) Distribution of the sum $\varphi = \Sigma\varepsilon_i$ of the three angles in ternary fission in the interaction of ^{238}U with 300 MeV ^{40}Ar [35]. b) Distribution of the angle ε between two fragments in ternary fission for the same reaction. The "model" is explained in the text (for further details see [35]).

in the calculations. The calculated angles of the "model" agree with the maximum of the observed distributions, thus indicating that the assumptions were reasonable.

2.4.3. Investigations Using the 4π-Geometry Method with $ThSiO_4$-Crystals

An ideal system for the investigation of ternary fission is one in which the target atoms are distributed as finely as possible within the fragment detector matrix. Such a system is realized in synthetic $ThSiO_4$-crystals. Thorium serves as the target atom, and fission fragment tracks can be made visible within the crystal by etching it at 220 °C with phosphoric acid. Binary (B) and ternary (T) fission events are visible under an optical microscope after this etching, which is done when at least one fission fragment has penetrated the crystal surface (Fig. 18). In this case it is obvious that all the tracks of a fission event originate from one point. Due to conservation of momentum binary fission events cannot be colinear.

The first investigations using $ThSiO_4$ were carried out by *Fleischer*, *Price*, *Walker*, and *Hubbard*, using 414 MeV argon ions. They proved that events such as those shown in Figure 18 are genuine examples of ternary fission. They also determined the ratio for $\sigma(T):\sigma(B)=(3.3\pm0.3):100$ (Table 3). Furthermore, they calculated the angular distribution of fission tracks in the center-of-mass system, from the observed angular distribution of tracks (assuming that all ternary fission fragments have a mass of $A=89$). This is shown in Figure 19. The distribution is symmetrical around the angle of 90°—a consequence of compound nuclei formation. The most surprising result which can be drawn

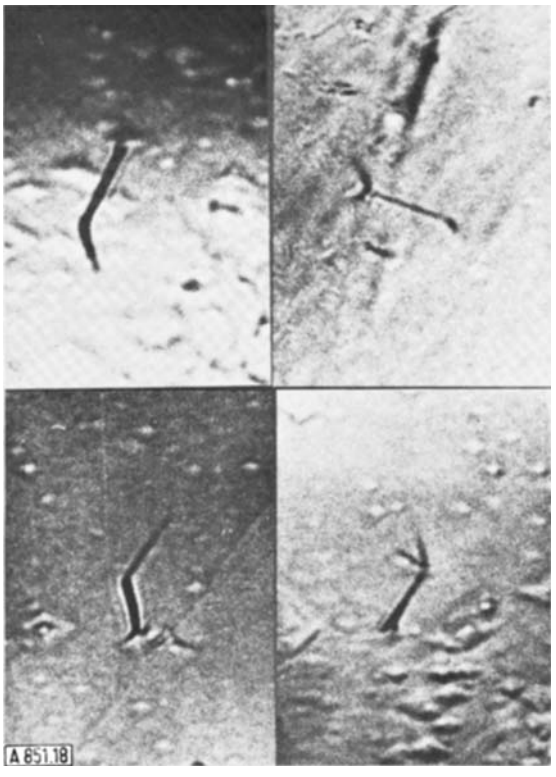


Fig. 18. Photomicrography of binary and ternary fission in thorium induced by 305 MeV Ar ions and registered in $ThSiO_4$ crystals.

from Figure 19, however, is that many tracks go either in the direction of the incoming argon ion or exactly in the opposite direction.

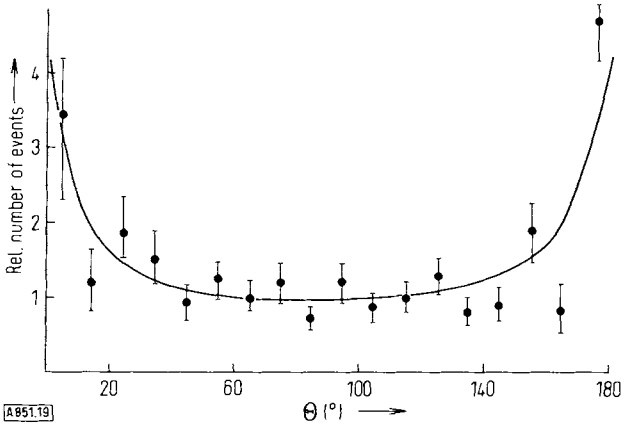


Fig. 19. Distribution of angles θ between fission fragments and the direction of the incoming Ar ions in the centre-of-mass system for the reaction Th + 414 MeV Ar [31].

The exciting results obtained by *Fleischer et al.* proved to be reproducible and are listed in Table 3[37, 38]. The angular distribution shown in Figure 19 could also be reproduced[38].

A small sample of $ThSiO_4$-crystal was irradiated in a test experiment with 300 MeV Ca-ions. One ternary and 116 binary fission events were observed[38], thus showing that such studies are feasible with Ca-ions also.

Unfortunately, it has not been possible to find other heavy-metal crystals displaying comparable properties to those

Table 3. Ratio of $\sigma(T):\sigma(B)$ in the reaction $^{232}Th + ^{40}Ar$, using $ThSiO_4$-crystals.

Ar-ion energy (MeV)	$\sigma(T):\sigma(B)$	Ref.
414	$(3.3\pm0.3):100$	[31]
300	$(2.0\pm0.5):100$	[37]
300	$(0.7\pm0.4):100$	[38]

of $ThSiO_4$. A further aim in this field is the development of target-systems which can be irradiated with heavy ions such as Kr or Xe obtained from recently completed accelerators. One such detector might be Cd-doped AgCl-crystals[39].

3. Theory and Outlook

3.1. Direct Ternary Fission and Cascade Fission

The phenomenon of ternary fission has not been studied systematically from a theoretical point of view. To date, only *Muzychka et al.*[40] have suggested a reasonably plausible model. Figure 20 illustrates the two decay modes proposed for ternary fission, namely:

1. *Direct ternary fission:* Target and projectile form a compound nucleus which decays in *one* step into three fragments of approximately equal size. *Muzychka et al.*[40] have not developed a model for the calculation of this decay channel. Only one paper, written by *Greiner* and co-workers[41], is known to have been published regarding such a model. These authors claim that the compound nucleus oscillates into many possible forms, some of which are oblate. It is feasible that such oblate forms may decay more naturally into three particles than do prolate forms.

2. *Cascade fission:* The first step of this kind of fission is the asymmetrical decay of the compound nucleus into one light and one very heavy fragment with $A \simeq 200$. When this heavy fragment has a sufficiently high excitation energy, it may decay once more into two fragments, within a period of $\tau \simeq 10^{-21}$ seconds. Such a total decay process would yield three fragments in two steps.

The probability of this last step can be calculated if some fairly reasonable assumptions are made. The details are described in Reference [40]. However, two facts must be kept in mind, before these results can be discussed:

1. When *Muzychka et al.*[40] carried out their calculations in 1967, the mass-yield curves for only two heavy ion induced fission reactions were known experimentally ($U + ^{22}Ne$ and $Au + ^{12}C$). Obviously, the heavy branch of the mass-yield curve ($A > 190$) enters substantially into the calculations. However, the calculated ternary fission cross-section turned out to be too small for this reaction:

Reaction: ^{238}U + 185 MeV $^{22}Ne \longrightarrow$ fission

$\sigma(T):\sigma(B) = 10^{-4}:100$ (theory) (5)

$\sigma(T):\sigma(B) = (7.0\pm1.5)\cdot10^{-3}:100$ (experimental) (6)

2. In 1967 the mass-yield curve for argon-ion induced fission was unknown. *Muzychka et al.* estimated the yields for heavy fragments and then calculated a satisfactory agreement between theory and experiment for the reactions U + 270 MeV Ar, U + 310 MeV Ar, and Th + 414 MeV Ar[31,33]. Some years later, the mass-yield curves were determined experimentally for these same fission reactions[42–44]. As it turned out, *Muzychka et al.* had considerably underestimated the yield of heavy fragments; thus their agreement was to some extent fortuitous. It is hoped that future work will improve our understanding of ternary fission.

In this context it might be interesting to show the mass-yield curve for heavy ion induced fission reactions, as shown in Figure 21. Binary fission leads to a symmetry of the mass-yield curve around the mass $A_f = {}^1/_2$ [A (target) + A (projectile) − X neutrons]. This symmetry will necessarily be lost when ternary fission contributes appreciably to the

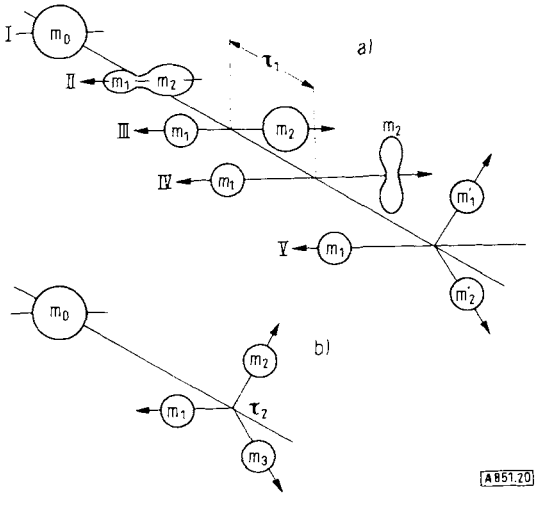


Fig. 20. Schematic representation of (a) cascade-type ternary fission [40] and (b) direct ternary fission [40].

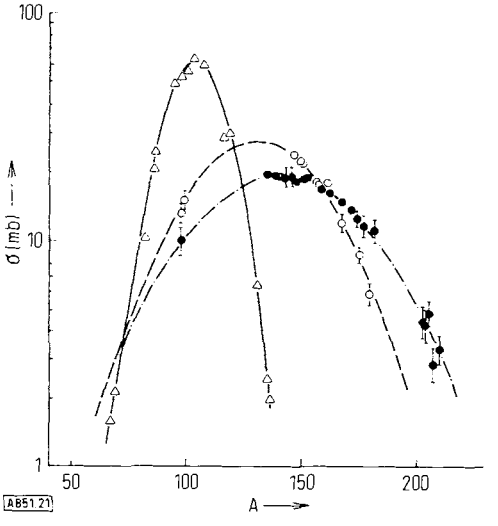


Fig. 21. Mass yield curve for various types of heavy-ion induced fission reactions. The experimental points were obtained by radiochemical methods and fitted to Gaussian-type distributions [44].
△: $Au + ^{12}C$; ○: $U + ^{20}Ne$; ●: $U + ^{40}Ar$.

total fission cross-section, giving a relative increase of light fragments as compared with heavy fragments. The experimentally known curves (Fig. 21) are, however, not determined accurately enough in order to show any such asymmetry. On the contrary, *Oganesyan* and co-workers were able to fit these curves to Gaussian distributions[43, 44].

3.2. The Production of Superheavy Elements ($Z \approx 114$) and the Phenomenon of Ternary Fission

A particular nuclear stability of the elements with $110 \leq Z \leq 120$ ("superheavy elements") has been predicted by a number of physicists during the last few years[45–48]. On the basis of these predictions, it is conceivable that superheavy elements might be so stable that they can be synthesized in a laboratory. It is also feasible that they exist in nature. However, for the production of superheavy elements in the laboratory, powerful new accelerators are needed which can accelerate ions as heavy as those of uranium up to such energies as to be able to induce nuclear reactions. Several such accelerators are under construction or have recently been completed. In the Federal Republic of Germany such an accelerator, called "UNILAC", is under construction by the "Gesellschaft für Schwerionenforschung, m. b. H.", near Darmstadt.

Several methods of producing superheavy elements have been discussed[49–53]. One such method, the fusion-fission method will be described here in some detail[53]. *Karamyan* and *Oganesyan*[53] assume that compound nuclei are formed in the interaction of uranium with uranium or xenon ions. The cross-section for such a complete fusion reaction is optimistically estimated to be 10^{-26}—10^{-25} cm^2 or 1—10% of the geometrical cross-section. These compound nuclei decay within approximately 10^{-21} sec by fission. *Karamyan et al.*[53] assume further that only two fragments are formed in fission. On the basis of the known fusion-fission mass-yield curves, as shown in Figure 21, the authors estimated the corresponding mass-yield curves for the reactions (U + U) and (U + Xe). It is plausible that one can expect very heavy fission fragments with $290 \leq A \leq 310$. Furthermore, one can estimate the upper limit for the production of a typical superheavy nuclide $^{A}Z = {}^{294}110$ as follows:

$$\sigma(^{294}110) \leq 10^{(30+1)}\ \text{cm}^2.$$

The production path can be summarized as follows:

$$^{238}\text{U} + {}^{238}\text{U} \rightarrow {}^{476}184 \qquad \text{(fusion to compound nucleus)} \quad (1)$$

$$^{476}184 \rightarrow {}^{294}110 + \text{(partners)} \qquad \text{(decay of compound nucleus)} \quad (2)$$

The limit for the ability to detect superheavy elements in such reactions will be approximately $10^{-(38\pm2)}$ cm^2, provided their half-lives are in the range of 10^{-9} sec $\leq \tau_{1/2} \leq 10^3$ a.

According to the calculations of *Karamyan* and *Oganesyan*, it should be possible to produce and detect superheavy nuclei. Unfortunately, these authors can only give an upper limit for the production cross-section, not a lower limit. This is connected in a twofold way with ternary fission:

1. The direct ternary fission process, as shown in Figure 20, has not been considered as a decay channel for the compound nucleus formed by fusion of uranium with uranium. Presently, it is impossible to estimate the relative importance of this decay channel as compared to others. But it cannot be excluded at all that, due to this factor, the production cross-section of superheavy elements will be decreased considerably.

2. The cascade fission process is also shown in Figure 20. It is quite feasible that the heavy fragment after the decay of the compound nucleus (Fig. 20, position III) is not spherical and unexcited but deformed and highly excited. *Karamyan* and *Oganesyan* assume that this heavy fragment de-excites itself essentially only by neutron and gamma emission, not by further fission. But this is not at all certain. *Swiatecki*[54] pointed out that the stability of superheavy nuclei against fission is restricted to spherical shapes and fairly low excitation energies. There exists a reasonable chance, therefore, that heavy fragments of the first binary fission process of the compound nucleus fission once more, thus giving rise to ternary fission and not to the production of superheavy nuclei. These considerations are presently the basis for extensive theoretical calculations. One example for calculations of the accesibility of superheavy nuclei is given by *Moretto et al.*[56]. Unfortunately, one cannot exclude the possibility that superheavy nuclei cannot be produced at all by fusion-fission reactions.

Nevertheless, all scientists associated with the problem of detecting superheavy elements *hope* that these elements can be produced with the new (and expensive) heavy-ion accelerators.

3.3. A Speculation on the Decay of Superheavy Elements and Possible Applications

It has been stated in this paper that, so far, superheavy elements have not been found anywhere and it is not clear whether they will be found in the future at all. Nevertheless, in conclusion it is worth speculating on possible radioactive decay modes for these undiscovered elements and on possible applications of them.

The alpha- and beta-decay of superheavy elements are not expected to exhibit any new and surprising characteristics. However, one expects some exciting features for spontaneous fission and neutron-induced fission of superheavy elements. The kinetic energy in spontaneous fission of superheavy nuclei will be approximately twice as large as for fission of uranium nuclei, but particularly important is the expectation that approximately 10—11 neutrons might be emitted per fission as compared with 2.5 neutrons in the fission of uranium nuclei[55]. In the case of ternary fission of superheavy elements, the number of neutrons per fission can be roughly estimated to be as high as 15.

It is well known that the critical mass of a nuclear assembly depends, very sensitively, on the number of neutrons per fission. The ratio of binary to ternary fission of superheavy elements will determine the average number of neutrons per fission and thus the critical size. A mixture of ^{235}U and sufficiently long-lived superheavy elements will then allow

the construction of any critical size within the limits given by the two pure components. A discussion of the technical and social consequences of this possible new application will not be entered into here.

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Application of Ligand Field Spectroscopy to Problems of Chemical Bonding in Solids[**]

By Dirk Reinen[*]

Selected examples (d^n systems) are presented to illustrate the interpretation of ligand field spectra (remission spectra) of solid inorganic compounds. In particular, this article demonstrates possible means for the investigation of weak cooperative interactions between transition metal coordination polyhedra and for the determination of the cation distribution in crystal lattices. The information value of the spectroscopic method to the chemist is critically discussed.

1. Introductory Considerations

If a free atom or ion is brought into a chemical environment of ligands, its energy levels undergo characteristic changes, which depend on the symmetry and strength of the "ligand field"[1,2]. The symmetry effect leads to splitting of some of these energy levels, while the strength of the electronic interaction between the central atom and its environment determines the degree of this splitting and of term shifts. In this progress report, we shall be concerned with transition metal coordination polyhedra, *i.e.* d^n systems. If one considers *e.g.* $3d^n$ cations in a ligand field of cubic symmetry, the five-fold degenerate d level splits into two, with energy differences Δ that very often correspond to absorption bands in the visible region of the spectrum. The optical d—d transitions that thus become possible are frequently the reason for the wide range of colors exhibited by the transition metal compounds. The cations of the elements of the lanthanum series are much less sensitive to environmental influences, owing to the much stronger shielding of the 4f electrons, while the available experimental data on 5f systems are scanty; moreover, the situation is more complicated, since the f level is split into three even in chemical environments of cubic symmetry, so that two ligand field parameters are required to describe these systems.

The MO scheme of a $3d^n$ cation in an octahedral environment of ligands that can form dative π bonds (*e.g.* F^-, O^{2-}) is shown in Figure 1. The orbitals of the central ion χ are shown on the left, while the linear combinations of the ligand orbitals φ, classified according to the symmetry of the octahedron O_h (symmetry-adapted), are shown on the right. For simplicity, sp_z hybridization of the ligand orbitals in the bond directions has been assumed, so that six functions lie on the sides of the ligands remote from the central ion, and may be disregarded as nonbonding. The electrostatic interaction of the central ion with its environment (Coulomb component C') and the overlap of the orbitals of the central atom with the appropriate linear combinations of the ligand orbitals (exchange component A') lead

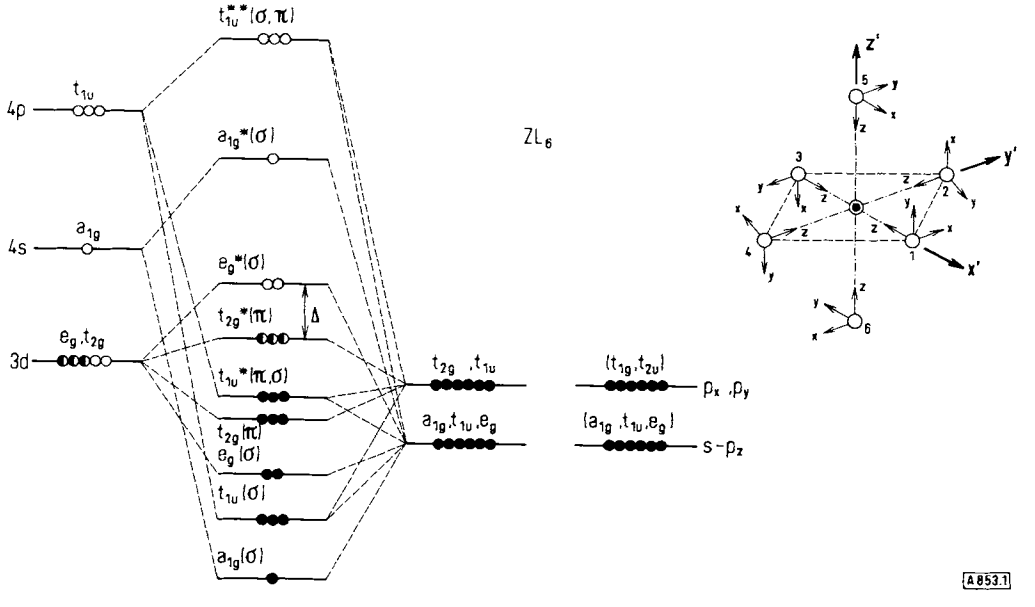


Fig. 1. Qualitative MO scheme of an octahedral transition metal complex ZL_6 (electron occupation corresponding to that of a CrF_6^{3-} octahedron). One of the three wave functions of the t_{2g}^{*} level ([eq. (2)]), for example, on the basis of the indicated coordinate systems is of the form: $\psi_t = \gamma d_{xy} - \delta(p_x^1 + p_y^2 + p_y^3 + p_x^4)$.

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to the bonding, nonbonding, and antibonding molecular orbitals indicated; we are particularly interested in the e_g^* and t_{2g}^* levels. If the wave functions describing these two MOs are[3]:

$$\psi_e = \alpha\chi_e^{(n)} - \beta\varphi_e^{(m)}; \quad \chi_e^{1,2}: d_{x^2-y^2}, d_{z^2} \tag{1}$$

$$\psi_t = \alpha\chi_t^{(m)} - \delta\varphi_t^{(m)}; \quad \chi_t^{1,2,3}: d_{xy}, d_{xz}, d_{yz} \tag{2}$$

then, to a rough approximation, Δ is given by[4]:

$$\Delta \approx [\int \chi_e H_L \chi_e d\tau - \int \chi_t H_L \chi_t d\tau] - [\beta \int \chi_e H_L \varphi_e d\tau - \delta \int \chi_t H_L \varphi_t d\tau] \tag{3}$$

where H_L is the energy operator characterizing the chemical environment and $d\tau$ is the infinitesimal volume element. Quantitative calculations[4] have shown that the Coulomb expression C' corresponding to the classical crystal field energy in the first set of brackets in eq. (3) is negative, and thus predicts that the e_g^* level will lie below the t_{2g}^* level, contrary to experimental findings. It is only with the "covalent" expression A' in the second set of brackets (negative), which gives the energy associated with the overlap between the orbitals of the central atom and of the ligands, that this effect is "overcompensated" so that the ligand field parameter Δ becomes positive (Fig. 2). It is clear from this greatly simplified consideration that electrostatic effects make only a minor contribution to the splitting of the d orbitals by a ligand field.

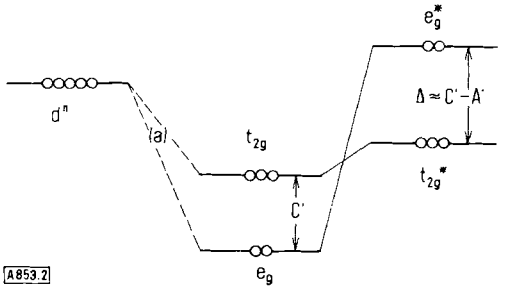


Fig. 2. Relative magnitudes of the "electrostatic" (Coulomb component C') and "covalent" (exchange component A') components of the parameter Δ that describes the splitting of the five-fold degenerate d state in an octahedral ligand field (qualitative picture—one-electron scheme).
(a) Coulomb interaction energy between d^n cation and ligands (spherically symmetrical and d-specific component).

The parameter Δ can be easily determined experimentally from the ligand field transitions between the e_g^* and t_{2g}^* levels. It further follows from the foregoing discussion that Δ is a measure of the strength of the interaction between the central atom and the ligands, or more precisely of the component of this interaction that is due to the d electrons of the central atom. It increases with the strength of the σ bond and, in the case of dative π bonds from the ligand to the central atom, with decreasing strength of the π bond component; Δ can therefore yield information on the bonding. In the spectrochemical series, the ligands are arranged in order of their "Δ effect"[1,2]. C and N always induce very large Δ parameters, whereas Br and I give quite small Δ parameters.

We have so far remained within the one-electron model, *i.e.* the electrostatic interactions between the d or the e_g^* and t_{2g}^* electrons were not considered. This "interelectronic interaction" can be described by additional energy quantities; in the case of d electrons, this is usually done by the Racah parameters B and C[1,2,5]. Figure 3 shows the spectra of the Ni^{2+} and Co^{2+} ions in an octahedral oxygen environment, together with the theoretical (electrostatic "crystal field model") band positions. As is immediately evident, the additional consideration of the interelectronic repulsion not only increases the number of terms, and hence also the number of possible transitions, but also

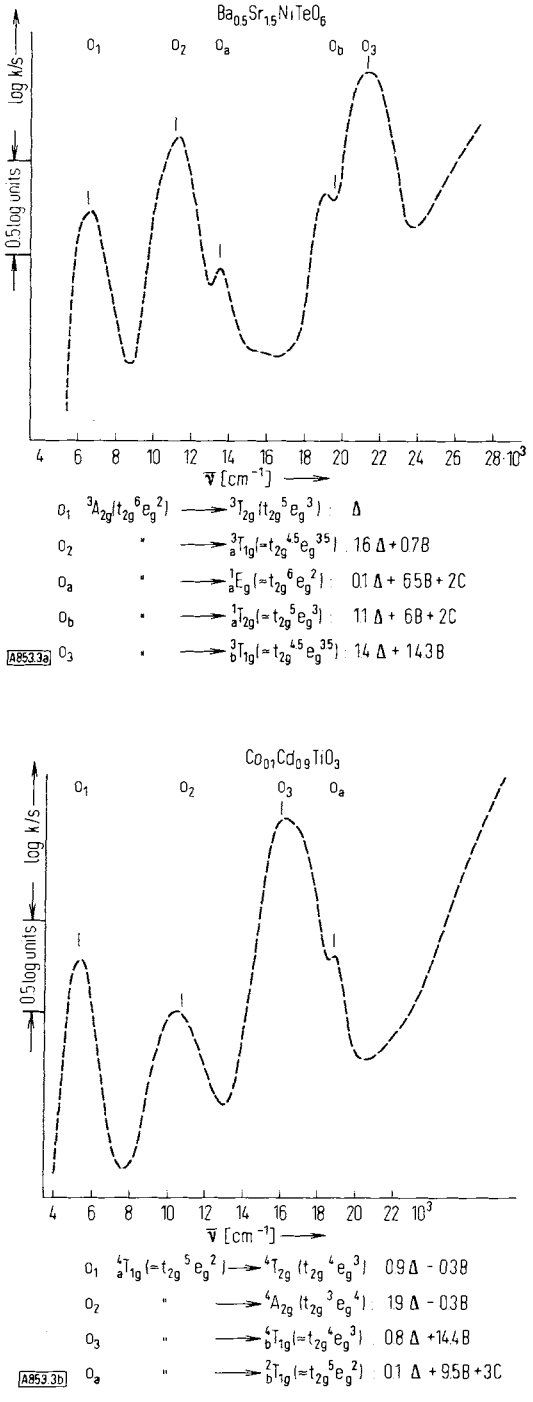


Fig. 3. Remission spectra of the Ni^{2+} ion (a) in a perovskite ordered in the octahedral sites $(Ba_{0.5}Sr_{1.5})^{(12)}(NiTe^{VI})^{(6)}O_6$ (band positions matched with $\Delta = 6500\ cm^{-1}$; $B = 860\ cm^{-1}$; $C/B = 4.2$; "nephelauxetic ratio" $B/B_0 = 0.83$) and of the Co^{2+} ion (b) in a host lattice of the ilmenite type $(Co_{0.1}Cd_{0.9}Ti)^{(6)}O_3$ ($\Delta = 5500\ cm^{-1}$; $B = 770\ cm^{-1}$; $C/B = 4.5$; $B/B_0 = 0.79$), together with the theoretical band positions (for $\Delta/B \approx 7.5$); octahedral coordination in each case [6].

causes mixing of one-electron states, so that configurations $t_{2g}^m e_g^n$ with non-integral m and n result.

For Ni^{2+}, for example, there are only two possible electron jumps in which the electron spin ($S=1$) is retained (triplet-triplet transitions): $t_{2g}(\uparrow\downarrow\ \uparrow\downarrow\ \uparrow\downarrow)\, e_g(\uparrow\ \uparrow) \rightarrow t_{2g}(\uparrow\downarrow\ \uparrow\downarrow\ \uparrow)\, e_g(\uparrow\downarrow\ \uparrow)$ or $t_{2g}(\uparrow\downarrow\ \uparrow\ \uparrow)\, e_g(\uparrow\downarrow\ \uparrow\downarrow)$; on the other hand, three principal bands o_1, o_2, and o_3 are observed. Moreover, the excited states to be correlated with the bands o_2 and o_3 are pronounced mixtures of one-electron functions with $m \approx 4.5$ and $n \approx 3.5$ (Fig. 3). The additional weak transitions (spin forbidden) o_a and o_b proceed with a change in the spin quantum number (triplet-singlet bands), and can be described approximately by: $t_{2g}(\uparrow\downarrow\ \uparrow\downarrow\ \uparrow\downarrow)\, e_g(\uparrow\ \uparrow) \rightarrow t_{2g}(\uparrow\downarrow\ \uparrow\downarrow\ \uparrow\downarrow)\, e_g(\uparrow\downarrow)$ and $t_{2g}(\uparrow\downarrow\ \uparrow\downarrow\ \uparrow)\, e_g(\uparrow\downarrow\ \uparrow)$.

It is now found that the parameters B and C calculated from the matching of the theoretical (crystal field model) band positions to the experimental positions are distinctly smaller than the values B_0 and C_0 found for the free d^n cations without a chemical environment. This depression should be due to covalent bonding, which has not yet been taken into account, and can be attributed partly to the extension of the electron cloud of the central atom towards the ligands on entry into a chemical bond and partly to the fact that the d electrons participate in the antibonding MOs with the fractions α and γ[7] [eq. (1), (2)][1,2] only. B and C should therefore decrease with increasing delocalization of the d electrons, *i. e.* with increasing "covalent character" of the bond in its d components. A rough idea of this effect is given by the "nephelauxetic series"[1,2], in which ligands are arranged according to the strength of their effect on B (and C).

The question now arises how far the theory outlined, which relates to individual complex units, is applicable to solids, in which the individual coordination polyhedra may be joined to one another by shared corners, edges, or even faces, and what deductions are possible in such cases. Compounds of the low-charge transition metal ions with ligands consisting of lighter atoms fortunately behave as if they consisted of *largely independent* complex units (cf. Fig. 3). The usual ligand field spectra are observed, though often with certain modifications, which are due to weak electronic effects extending beyond the individual coordination polyhedra. Weak "cooperative interactions" of this type are the subject of the following section. When we come to compounds such as FeS, NiSe, and NiAs, however, the d electrons are already extensively delocalized over the entire lattice. The electronic interactions between the individual coordination polyhedra have broadened the MOs of Figure 1 into bands, which fact usually leads to a total obliteration of the ligand field spectrum. Another important use of the ligand field spectroscopy of solid compounds is discussed in Section 3.

2. Influence of Weak Cooperative Effects on Ligand Field Spectra

Figure 4 shows the remission spectra of some compounds of the corundum type containing Cr^{3+}, in which the cations are octahedrally coordinated by oxygen, together with the theoretical band positions (crystal field treatment again) in multiples of Δ and B. First of all, it is clear that Δ, as measured by the position of the first band, decreases as the lattice is expanded. It is of no consequence here whether the expansion is due to Cr^{3+} or to Ga^{3+}, which are almost equal in size (α-$Cr_{0.1}Al_{1.9}O_3 \rightarrow Cr_2O_3$ or α-$Cr_{0.1}Ga_{1.9}O_3$). If, on the other hand, one considers the position of the second principal band, which is partly determined by the parameter B, distinct differences are found between Cr_2O_3 and α-Ga_2O_3 doped with Cr^{3+}. Whereas the B values of the latter compound and of α-Al_2O_3 containing Cr^{3+} are practically the same, B is much smaller in the case of Cr_2O_3[8]. The paramagnetic Cr^{3+} ions of different coordination polyhedra evidently "see" one another, *i. e.* delocalization effects of the d electrons—as indicated by the extremely low B-value—are operative beyond the individual CrO_6 polyhedra. This is in agreement with the antiferromagnetism of Cr_2O_3 as a result of spin-spin interaction between the Cr^{3+} ions of adjacent octahedra through shared faces.

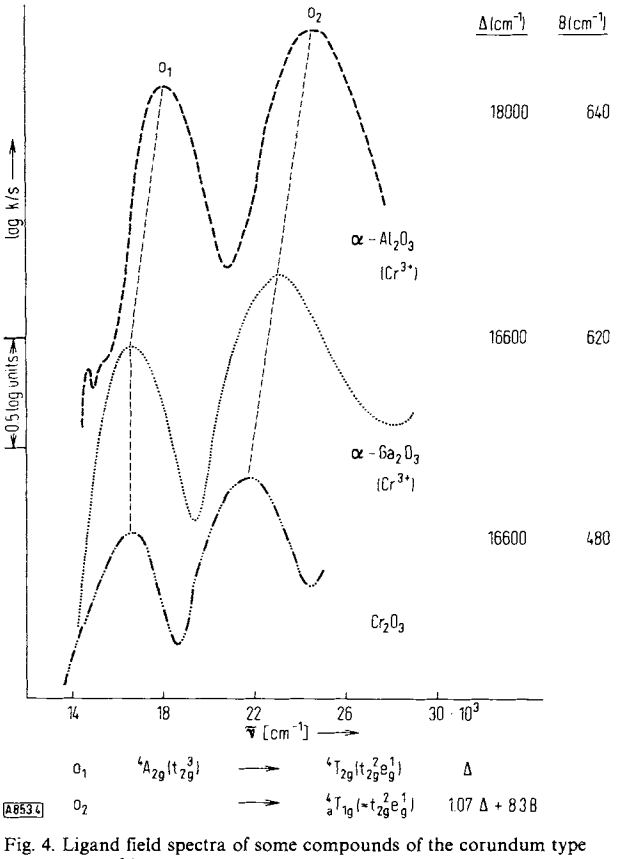


Fig. 4. Ligand field spectra of some compounds of the corundum type containing Cr^{3+} ($Cr_{0.1}Al_{1.9}O_3$, $Cr_{0.1}Ga_{1.9}O_3$, Cr_2O_3) and theoretical band positions (for $\Delta/B \approx 30$; only two of the three spin-allowed transitions are shown); octahedral coordination in each case.

A similar though weaker depression of the B values is found for the solid solution series $Ni_xMg_{1-x}O$[9] with NiO, which is also antiferromagnetic, as the final member. However, this series points to a further interesting effect. The spectra of the compounds with small values of x show the usual picture, with three strong bands (o_1, o_2, o_3), which correspond to triplet-triplet transitions, and a few triplet-singlet transitions (o_a, o_b, o_c), which are spin forbidden and therefore weak (Figs. 3a and 5). These latter transitions become stronger with increasing Ni^{2+} concentration,

until finally their intensities become at least comparable to those of the first three bands mentioned (Fig. 5). The antiferromagnetic interactions between the (S = 1) ground states of the Ni^{2+} ions of different octahedra evidently lead to a new "cooperative" singlet ground state, so that the previously spin-forbidden bands are now allowed (Fig. 6).

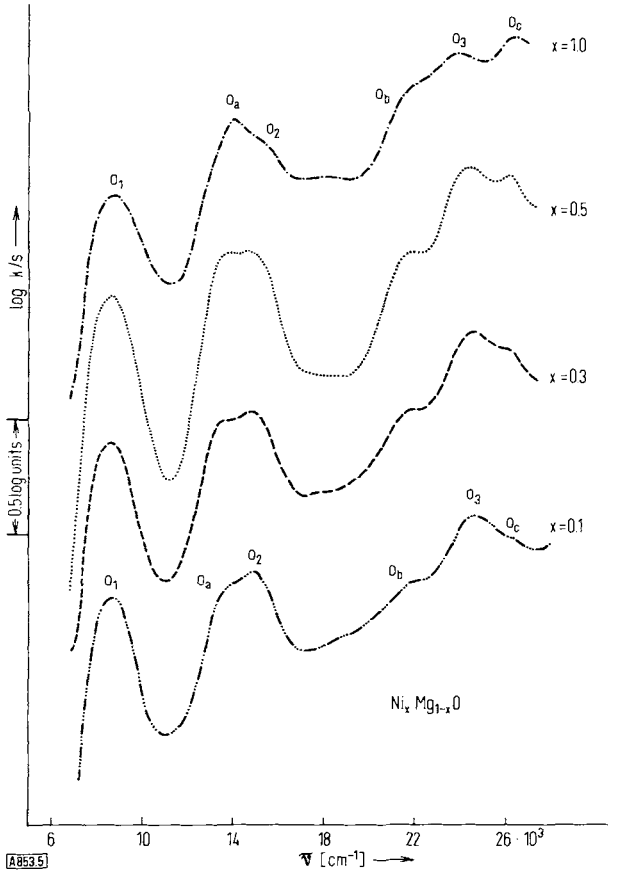


Fig. 5. Remission spectra of solid solutions $Ni_xMg_{1-x}O$ (NaCl structure).

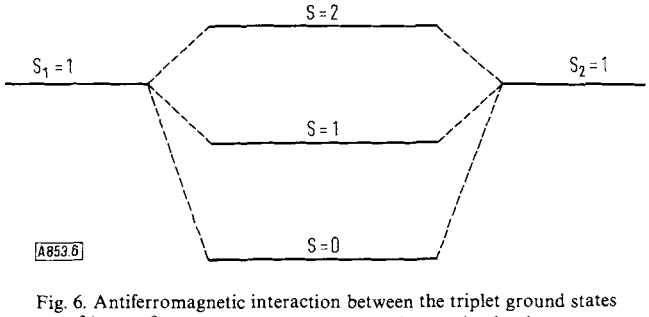


Fig. 6. Antiferromagnetic interaction between the triplet ground states of Ni^{2+} ions ($^3A_{2g}$) for the case of only two interacting levels.

A different kind of example of the effect of the cationic environment on the bonding in a transition metal coordination polyhedron is provided by perovskites which are ordered in the octahedral sites (elpasolite type) and have the structure and composition shown in Figure 7. Each Ni^{2+} ion is surrounded *via* its six oxygen neighbors by six M^{VI} cations. If M^{VI} is an ion having an inert gas configuration, such as W^{VI}, the ligand field parameters are about 25% higher ($\Delta = 8500\ cm^{-1}$) than for M^{VI} being an ion with a d^{10} configuration, such as Te^{VI} ($\Delta = 6600\ cm^{-1}$)[10]. Single crystal X-ray investigations have shown that the Ni—O distances are practically the same in both compounds, so that ionic size effects can be largely ruled out as a cause[11]. Since the *B* value (860 cm^{-1}), and hence the d covalence of the Ni—O bonds, is also the same in both cases, the σ and π components of the bonds are presumably different. W^{VI} should have a stronger π-polarizing effect and a weaker σ-polarizing effect on the linking oxygen ligands than Te^{VI}, which has little tendency to form π bonds because of its filled d shell. The result of this bond polarization would thus be stronger σ components and weaker π components of the Ni—O bonds, and hence a greater Δ for the tungsten perovskite. Similar investigations can also be carried out with other cations and for other host lattice structures[8, 10].

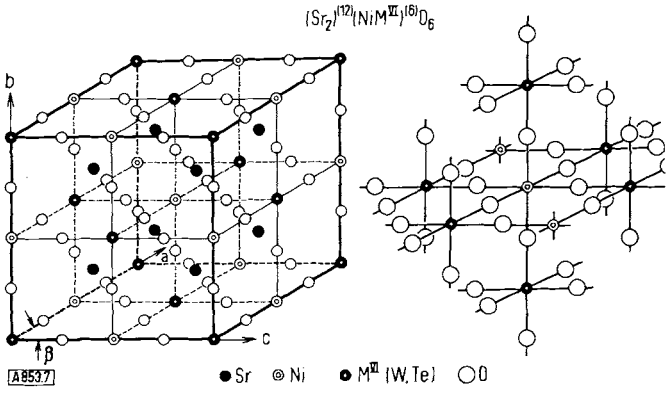


Fig. 7. Lattice structure (left) of perovskites ordered in the octahedral sites $(Sr_2)^{(12)}(NiM^{VI})^{(6)}O_6$ (idealized) and nearest cationic M^{VI} neighbors (right) of the Ni^{2+} ions in this lattice (elpasolite type).

Interesting aspects are also offered by the numerous compounds in which *one* transition element is present in *different* oxidation states. While the spectra of such mixed valence compounds are often simply the sums of the spectra of the constituent complex units, new bands frequently also appear, as in the case of the complex $Fe^{II}-Fe^{III}$ cyanides (*e.g.* Prussian blue and Turnbull's blue). It was uncertain for a long time whether Fe^{2+} and Fe^{3+} occupy fixed positions in these lattices or whether a rapid valence change occurs by transfer of an electron. It was shown with the aid of Mössbauer and ligand field spectroscopy[12] and from the results of magnetic measurements that almost total "charge localization" with octahedral $Fe^{II}C_6$ and $Fe^{III}N_6$ polyhedra must be assumed in all compounds of this type, Fe^{2+} having a low-spin configuration (t_{2g}^6) and Fe^{3+} a high-spin configuration ($t_{2g}^3e_g^2$). Thus the structure of "soluble Prussian blue" $KFe^{III}Fe^{II}(CN)_6$ can be described in the same way as the perovskites ordered in the octahedral sites (Fig. 7), with alternating occupation of the octahedral sites by Fe^{2+} and Fe^{3+} ions, which are linearly linked to one another *via* CN^- groups. The two "additional" bands in the spectrum of this compound can be interpreted as transitions of an electron from the $Fe^{II}C_6$ to the $Fe^{III}N_6$ term system. These transitions are the cause of the blue color, which is not characteristic of the two component polyhedra; appreciable electronic coupling between them may therefore be assumed. The two bands at

about 15000 and 25000 cm^{-1} can be approximately characterized as follows:

$$Fe^{II}\,t_{2g}^6\,(C) - Fe^{III}\,t_{2g}^3\,e_g^2\,(N) \quad (a)$$
$$\longrightarrow Fe^{III}\,t_{2g}^5\,(C) - Fe^{II}\,t_{2g}^4\,e_g^2\,(N) \quad (b)$$
$$\text{and} \longrightarrow Fe^{III}\,t_{2g}^5\,(C) - Fe^{II}\,t_{2g}^3\,e_g^3\,(N) \quad (c)$$

The energy difference ($\approx 10000\ cm^{-1}$), in agreement with the assignment made, corresponds to the position of the band found in the spectrum of octahedral $Fe^{II}N_6$ complexes for the transition: $t_{2g}^4 e_g^2 \rightarrow t_{2g}^3 e_g^3$. Finally, intensity calculations show that the ground state of the Fe ions in soluble Prussian blue is determined by *(a)* to an extent of 99%, while the contribution of the configuration *(b)* is only $\approx 1\%$, *i.e.* almost complete charge localization may in fact be assumed in the lattice.

The next example illustrates a further advantage of spectroscopic methods, *viz.* the possibility of specifically determining the symmetry of the environment of a transition metal cation that is present only in a very low concentration in a host lattice. It is well known that the ^2E_g ground state of the d^9 cation Cu^{2+} has a very high Jahn-Teller instability in octahedral coordination[13, 14]. As is illustrated by Figure 8, this level can be split by distortion of the coordination octahedron (tetragonal in the simplest case), and electronic energy thus be obtained (energetic aspect of the Jahn-Teller effect).

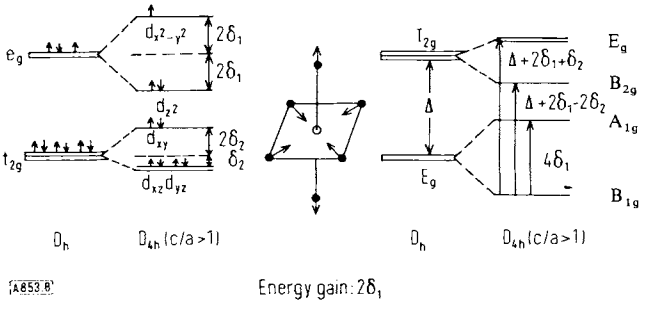


Fig. 8. Demonstration of the Jahn-Teller effect for Cu^{2+} (d^9) in an octahedral environment (moderately strong tetragonal ligand field component—expansion in two and compression in four directions). Left: one-electron scheme, right: many-electron scheme.

The extent of this splitting $4\delta_1$ will increase with the magnitude of the tetragonal ligand field component, and hence with the distortion of the CuL_6 octahedron. Even if the distortion of the octahedron is of a symmetry lower than tetragonal, the tetragonal component normally dominates, and nearly always corresponds to an elongation in two Cu—L directions and a compression in the plane perpendicular to these, as is assumed in Figure 8. If Cu^{2+} ions are incorporated isomorphously into host lattice structures, *e.g.* instead of Zn^{2+} (Zn being adjacent to Cu in the periodic table), the ligand field spectrum is "tetragonal" even at low Cu^{2+} concentrations. It is characterized by three bands instead of the single transition expected for O_h symmetry (Fig. 8), even when there is not yet any macroscopic effect (decrease in the symmetry of the host lattice) to be observed (Figs. 10 and 11)[15]. The distortion of *e.g.* CuO_6 polyhedra indicated by the ligand field spectrum at very low Cu^{2+} concentration is "dynamic"[14, 16], *i.e.* the long, preferred axis of the octahedron changes between the three possible directions (Fig. 9), so that, in a time average an undistorted octahedron results (ESR spectroscopic result). When a certain limiting concentration of Cu^{2+} ions is

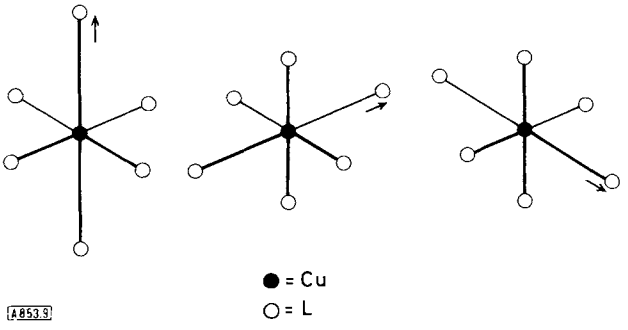


Fig. 9. Dynamic Jahn-Teller effect of "tetragonally elongated" CuL_6 octahedra (directions of axes time dependent).

reached, cooperative elastic interactions between the individual CuO_6 polyhedra in the lattice lead to a fixation and energetically favorable orientation of the long axes of the CuO_6 units in relation to one another (static Jahn-Teller effect), and hence to a macroscopic symmetry effect of the host lattice structure (X-ray result). While these last data cannot be obtained from the ligand field spectrum, this nevertheless provides other information. If Cu^{2+} ions are incorporated into host lattice structures characterized by a layer structure as shown in Figure 10[17], one observes tetragonal distortions of the CuO_6 coordination poly-

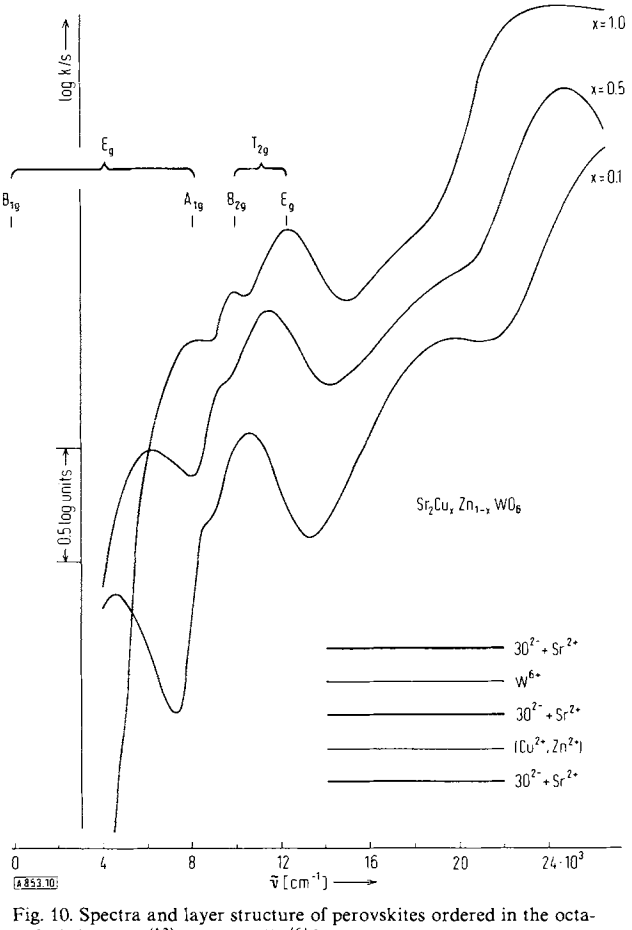


Fig. 10. Spectra and layer structure of perovskites ordered in the octahedral sites $(Sr_2)^{(12)}(Zn_{1-x}Cu_xW)^{(6)}O_6$.

hedra, which increase with increasing Cu^{2+} concentration as is indicated by the measured E_g splitting (position of the lowest-energy ligand field band)[15]. The spectroscopic result seems understandable, since on the one hand the layers consisting *exclusively* of bivalent cations possess great geometric flexibility, while on the other hand the tetragonal distortion of the CuO_6 octahedra should increase with decreasing number of ZnO_6 octahedra which occupy equivalent lattice sites and hence must also be distorted. If, however, bivalent cations and cations of higher charge are mixed in the same layer, as in the trirutile lattice, the splitting of the E_g ground state is independent of the Cu^{2+} concentration, and remains small (Fig. 11)[15]. The highly charged, and hence strongly structure-determining, Sb^{5+} ions evidently oppose any distortion of their environment, so that the geometric conditions in this case are unfavorable for a maximum Jahn-Teller deformation.

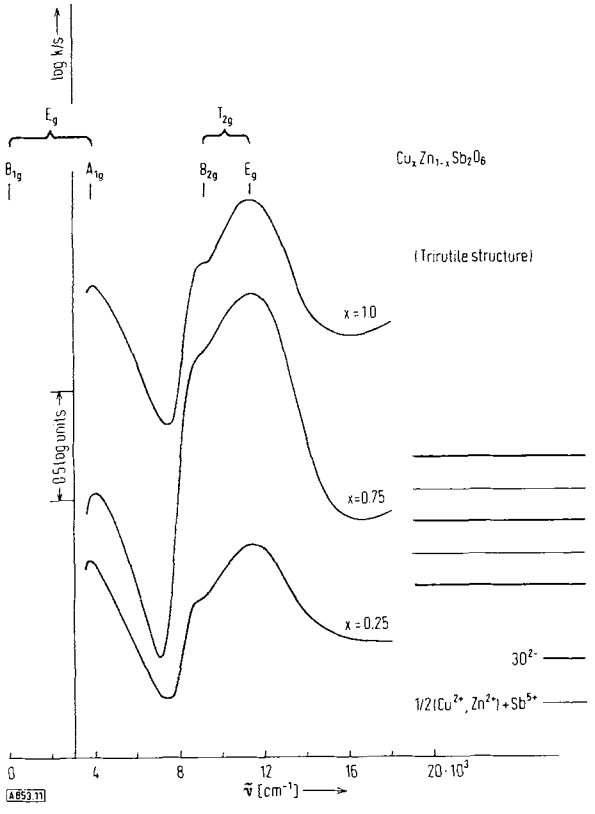


Fig. 11. Spectra and layer structure (highly idealized) of trirutile phases $(Zn_{1-x}Cu_xSb_2)^{(6)}O_6$.

Let us now briefly consider the question of the geometric patterns in which distorted CuL_6 octahedra are arranged with respect to one another within a lattice for a few simple cases. In the case of the spinel structure, for example, in which the Jahn-Teller distorted coordination octahedra are joined to one another exclusively by shared edges, the elastic interactions between these polyhedra should proceed *via* these shared edges. The energetically most favorable geometric arrangement for this case is the pattern of Figure 12, corresponding to tetragonal distortion of the lattice with $c/a>1$[18, 19]. In the perovskite structure ABL_3, on the other hand, there are only corner-linked octahedra, and the energetically most favorable interactions lead to a tetragonal deformation with $c/a<1$ (Fig. 13)[19]. In this arrangement, long and short Cu-ligand distances alternate in two lattice directions, while the third direction has only short distances. If the $M^{VI}O_6$ unit in the ordered perovskite structure (Fig. 7) is now regarded as *one* extended ligand L, the lattice may be regarded as consisting of edge-linked and corner-linked CuL_6 octahedra. As expected, the interaction *via* the edges, which is determined by the shorter distances, dominates here, and this leads, for compounds having the composition $Sr_2(CuM^{VI})O_6$, to tetragonal lattices with $c/a>1$[15, 21]. Compounds $A^I_2[M^{II}Cu](NO_2)_6$ [A^I: K^+, Tl^+, Rb^+, Cs^+; M^{II}: Ca^{2+}, Sr^{2+}, Ba^{2+}], whose structures can be described in almost the same way[20, 23], also crystallize tetragonally with $c/a>1$. If however the alkaline earth metal ions M^{II} are replaced by Pb^{2+}, cubic structures determined by a dynamic Jahn-Teller effect are observed at higher temperatures[20, 22], which change very

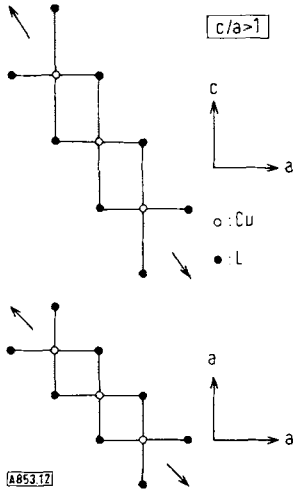


Fig. 12. Elastic interactions between "tetragonally elongated" CuL_6 octahedra with common edges leading to a tetragonal lattice distortion with $c/a>1$.

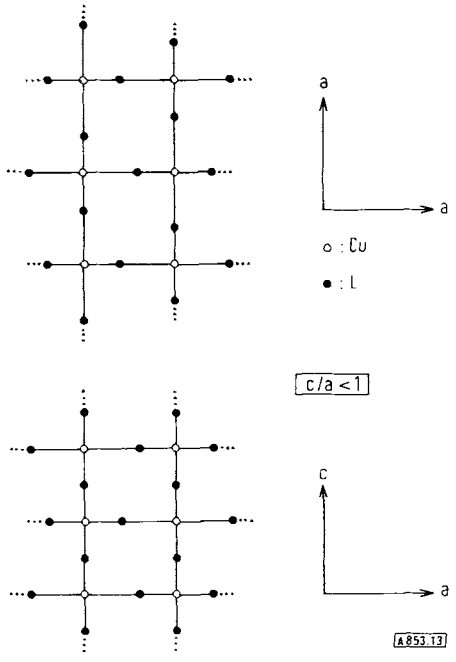


Fig. 13. Elastic interactions between corner-linked "tetragonally elongated" CuL_6 octahedra leading to a tetragonal lattice distortion with $c/a<1$.

soon into tetragonal lattices with $c/a<1$ when the temperature is lowered (high and low temperature Guinier techniques)[20, 24]. It is possible that the substitution of the M^{II} ions with inert gas configurations by the covalent Pb^{2+} ion with a $d^{10}s^2$ configuration increases the elastic-cooperative interactions *via* the corners of the octahedra (more precisely *via* the linear $NO_2—M^{II}—O_2N$ bridges) to such a degree that the mechanism of Figure 13 predominates over that of Figure 12. This last example has also marked a limit for the information value and sensitivity of the ligand field spectra. Whereas the charge transfer spectra[22, 25] as well as the ESR spectra[20] of the alkaline earth metal and Pb^{II} compounds show distinct differences, the ligand field spectra do not record the alteration of the M^{II} ion and hence the difference in the cooperative Jahn-Teller order[20]. Finally, this example shows that cooperative phenomena in solids should not be investigated by a single method, but require the use of a number of mutually complementary methods if useful information is to be obtained.

3. Ligand Field Spectroscopy and Cation Distribution in Solids[6]

Another very important use of ligand field spectroscopy is the qualitative to semiquantitative determination of the cation distribution in crystal lattices. If a transition metal ion can occupy sites of different coordination numbers in a host lattice (*e.g.* spinel or garnet structure), the ligand field spectrum rapidly provides information on how this possibility has been utilized. The cation distribution can also be analyzed with the aid of ligand field spectra in the case of lattice sites having the same coordination number but sufficiently different Δ values (*e.g.* olivine and enstatite structures). The following discussion will be confined to cases in which *octahedrally* and *tetrahedrally* coordinated lattice sites compete with one another. Figure 14 shows sections of the MO schemes for octahedrally and tetrahedrally coordinated d^n cations with the partly occupied antibonding levels which we are interested in. The energy positions of the t_2^* and e^* orbitals are inverted for the tetrahedron compared to the octahedron, and the ligand field parameter Δ_t (for the same ligands) is only about half as great as Δ_o[26]. The spectrum of a tetrahedrally coordinated d^n cation thus mostly appears at longer wavelengths than that of the octahedrally coordinated cation. For example, if a transition metal ion occupies octahedral as well as tetrahedral sites in the spinel lattice $A^{(4)}B_2^{(6)}O_4$, Fe^{2+} spectra show octahedral and tetrahedral bands clearly separated from each other, whereas these transitions partly overlap for the Ni^{2+} ion[27] (Figs. 15 and 16).

Interesting further information on the cation distribution is provided by estimates of the "ligand field stabilization energies" produced by the particular d^n occupation (one-electron model without consideration of the interelectronic repulsion—"high-spin configuration")[6, 28, 29]. If the t_{2g}^* and e^* levels (Fig. 14) are taken as arbitrary zero energy levels, we find the values given in Table 1 for the relative destabilizations for octahedral and tetrahedral coordination as a function of n[6, 29]. These specific d-electron contributions are responsible *e.g.* for the fact that the lattice energies of fluorides MF_2 ($M=3d^n$ cation) do not exhibit the expected linearity as a function of n[1]. The differences between the octahedral and tetrahedral stabilization energies with $\Delta_o \simeq 2\Delta_t$ should be a *relative measure* of the preference of an octahedral to a tetrahedral environment or *vice versa* for a d^n cation (Table 1). They should be the deciding factor for the site preference when one considers a sequence of cations that differ only very slightly, if at all, in all the parameters that influence bonding (principal quantum number, ionic charge and size, *etc.*) except in

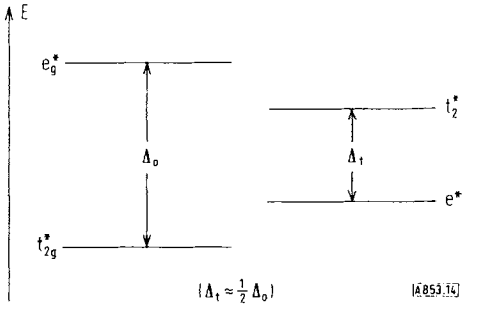


Fig. 14. The antibonding MOs for octahedral and tetrahedral ligand fields which are largely determined by the d orbitals of the central atom (sections from the corresponding MO schemes).

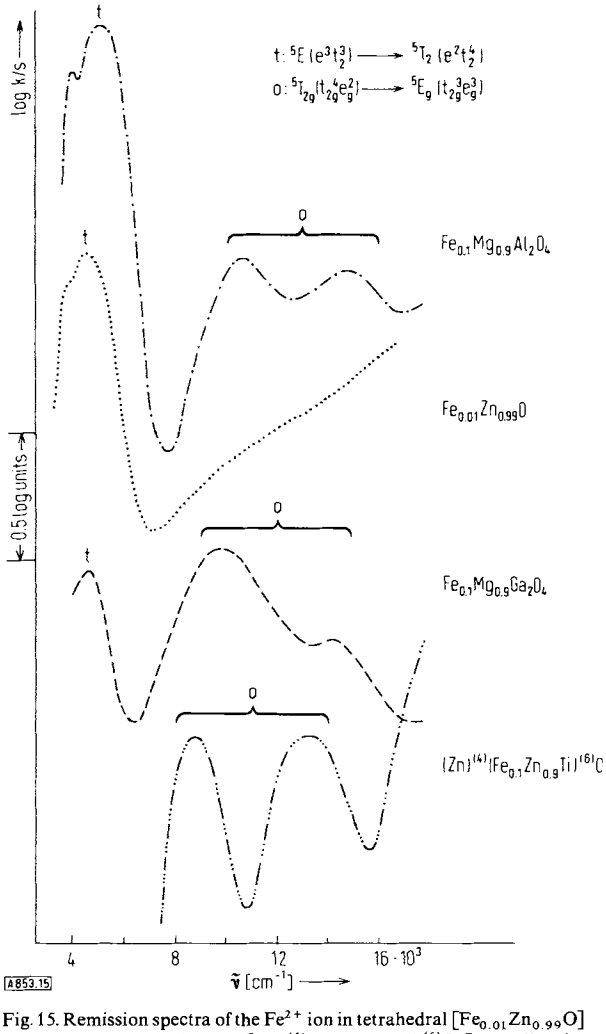


Fig. 15. Remission spectra of the Fe^{2+} ion in tetrahedral $[Fe_{0.01}Zn_{0.99}O]$ and octahedral coordination $[(Zn)^{(4)}(Fe_{0.1}Zn_{0.9}Ti)^{(6)}O_4]$ as well as for cases of a distribution over tetrahedral and octahedral lattice sites (arbitrary intensity scale—wurtzite and spinel structures).

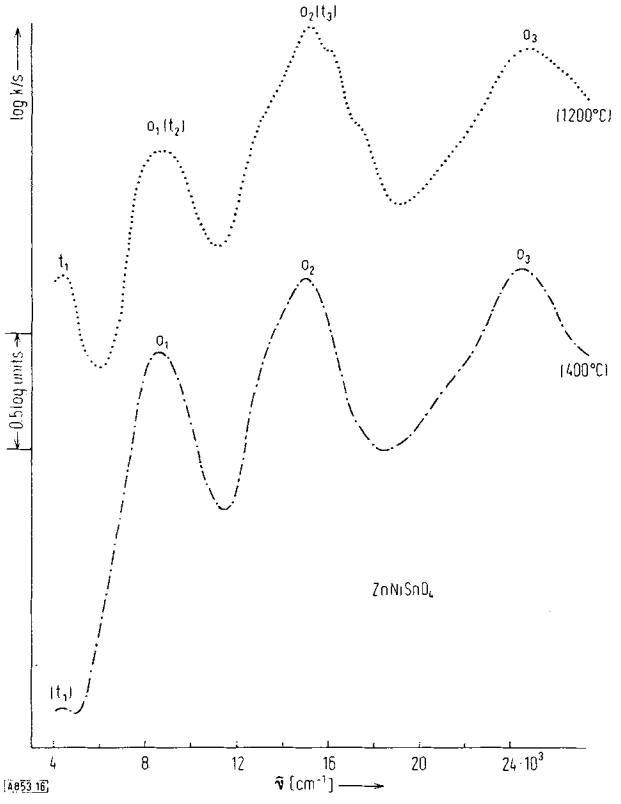


Fig. 16. Remission spectra of the Ni^{2+} ion in the spinel $ZnNiSnO_4$ at different equilibrium temperatures.

the number of d electrons (provided, naturally, that the ligands are the same). These "site preference energies" are energetically relative, since the zero energy levels chosen for the octahedral and tetrahedral stabilization energies (Fig. 14) are different. Even if π bonds are negligible, as may be assumed for the spinel lattice[6], the Coulomb energies are not the same[30]. However, a considerable amount of information can be obtained from these relative "site preference energies". Thus cations having a d^{10} configuration should favor the tetrahedral configuration, while d^3 cations should favor the octahedral configuration. $Ni^{(4)}Cr_2^{(6)}O_4$ is in fact a normal spinel with exclusively octahedral coordination of the Cr^{3+} ions, while $NiGa_2O_4$ has the inverted cation distribution $Ga^{(4)}(NiGa)^{(6)}O_4$, the Ni^{2+} ions evidently being totally displaced into the octahedral sites of the lattice by Ga^{3+}. These distributions can be established quantitatively from the ligand field spectra, since only tetrahedral Ni^{2+} bands are found in the former case and only octahedral bands in the case of $NiGa_2O_4$. Another example is provided by the spectra of Figure 15. The replacement of the Al^{3+} ions in the spinel $Fe_{0.1}Mg_{0.9}Al_2O_4$ by Ga^{3+} leads to a very pronounced decrease in the intensity of the tetrahedral Fe^{2+} absorption in relation to the octahedral absorption, since the d^{10} Ga^{3+} ions, as expected, displace Fe^{2+} ions from tetrahedral into octahedral sites. Nevertheless, a considerable concentration of tetrahedrally coordinated Fe^{2+} ions remains. Ga^{3+} evidently does not block the tetrahedral holes to Fe^{2+} as extensively as to Ni^{2+}, again in agreement with the δ energies of Table 1, which hint at a stronger preference for octahedral coordination in the case of d^8 cations than for d^6 cations.

Table 1. Ligand field stabilization energies of d^n cations (high-spin configuration) for octahedral (E_o) and tetrahedral coordination (E_t) as well as relative site preference energies ($E_o - E_t = \delta$, with $\Delta_o \approx 2\Delta_t$). (One-electron energies without consideration of interelectronic repulsion.)

n		E_o			E_t	δ
1, 2	$t_{2g}^{1,2}$	0	$e^{1,2}$		0	0
3	t_{2g}^3	0	e^2	t_2^1	$-\Delta_t$	$+\frac{1}{2}\Delta_o$
4	t_{2g}^3 e_g^1	$-\Delta_o$	e^2	t_2^2	$-2\Delta_t$	0
5, 6, 7	$t_{2g}^{3,4,5}$ e_g^2	$-2\Delta_o$	$e^{2,3,4}$	t_2^3	$-3\Delta_t$	$-\frac{1}{2}\Delta_o$
8	t_{2g}^6 e_g^2	$-2\Delta_o$	e^4	t_2^4	$-4\Delta_t$	0
9	t_{2g}^6 e_g^3	$-3\Delta_o$	e^4	t_2^5	$-5\Delta_t$	$-\frac{1}{2}\Delta_o$
10	t_{2g}^6 e_g^4	$-4\Delta_o$	e^4	t_2^6	$-6\Delta_t$	$-\Delta_o$

Finally, the temperature dependence of cation distributions can also be followed spectroscopically. Whereas the spinel $ZnNiSnO_4$ has a practically normal cation distribution $Zn^{(4)}(NiSn)^{(6)}O_4$ at low temperatures, as can be seen from Figure 16, a higher equilibrium temperature leads to a migration of the Zn^{2+} ions (d^{10}) from tetrahedral to octahedral sites and of Ni^{2+} ions (d^8) in the opposite direction. This can be deduced from the increase in intensity of the tetrahedral band t_1 in the spectrum (Fig. 16) for example, and corresponds to the tendency of the d^n cations to migrate into the energetically less favored coordination when energy is supplied[26]. This completes our discussion of questions of cation distribution. Further examples, also with different host lattice structures, may be found in [6].

Concluding, it is to be stated that ligand field spectra of single crystals naturally provide more extensive information than those of crystalline powders, particularly in connection with intensity problems or low symmetry effects. However, the information value of remission spectra to the chemist should not be underestimated, particularly when one considers the ease with which such spectra are obtainable.

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[24] Whereas the K and Tl compounds are still cubic at 298 °K, the Rb and Cs compounds crystallize tetragonally with $c/a<1$ at this temperature already [20].

[25] Charge transfer bands correspond to transitions from nonbonding or bonding MOs to the t_{2g}^* or e_g^* levels (Fig. 1), and usually occur at shorter wavelengths than the ligand field bands.

[26] It should also be mentioned that the intensity of the "tetrahedral absorption" is greater by approximately one order of magnitude than that of the "octahedral absorption"; changes in the occupation density of tetrahedral lattice sites are therefore recorded more sensitively by the ligand field spectrum than changes in the occupation of octahedral positions.

[27] This is a consequence of the fact that the positions of the principal bands in the case of Ni^{2+}, unlike in the case of Fe^{2+}, are determined not only by Δ but also by the Racah parameter B (Fig. 3), which has practically the same value for octahedral as for tetrahedral coordination.

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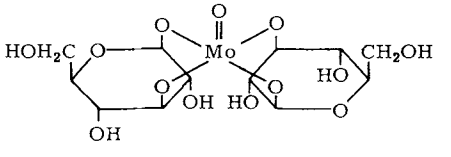
[30] The electrostatic stabilization of an octahedrally coordinated ion in a crystal lattice (Madelung energy) is generally greater than that of a tetrahedrally coordinated ion, so that the site preference energies (δ in Table 1) would become more positive as a result of a correction in this sense, in agreement with the structural observation that among the oxides VO, MnO, FeO, CoO, NiO, and ZnO, only the last crystallizes with tetrahedral MO_4 units.

COMMUNICATIONS

Epimerization of Carbohydrates Catalyzed by Molybdate Ions

By *Vojtech Bilik*, *Wolfgang Voelter*, and *Ernst Bayer*[*]

All aldopyranoses having free hydroxyl groups on C-1 to C-3 react with molybdate ions[1]. The resulting sugar-molybdate complexes have hitherto been used in configurational and conformational analysis of carbohydrates by circular dichroism measurements. We have now found a new sugar synthesis involving these complexes as intermediates. Heating of, *e.g.* D-glucose with molybdic acid in aqueous solution for several hours affords D-mannose in 25% yield. This epimerization can be explained in terms of formation of a glucose-molybdate complex of structure *(1)*.

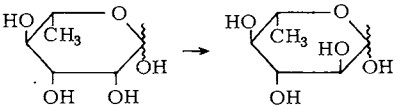


(1)

Our studies have shown that epimerization of L-rhamnose *(2)* with molybdic acid gives 60% of L-chinovose *(3)* *via* the L-rhamnose-molybdate complex.

This sugar was previously prepared only in poor yield by multistep syntheses[2]. Other rare sugars, *e.g.* D-talose from D-galactose[3], also become readily accessible in good yields by this epimerization.

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(2) *(3)*

L-*Chinovose (3)*:

A mixture of L-rhamnose *(2)* (100 g), molybdic acid (1 g), and water (500 ml) is heated to 95 °C for 3 h. Filtration is followed by deionization with a basic ion exchanger and subsequent evaporation under reduced pressure to give a syrup, which is dissolved in anhydrous ethanol and again evaporated to dryness. The syrup is dissolved in anhydrous ethanol (100 ml) and treated in the warm with ethyl acetate (200 ml). L-Chinovose *(3)* (33 g) crystallizes at room temperature. The filtrate is concentrated and again epimerized as described above to give a further yield of *(3)* (20 g). By reaction of the second filtrate obtained it was possible to isolate a further 13 g of *(3)*. The sugar is recrystallized from anhydrous ethanol (m.p. 151 °C, $[\alpha]_D^{24} = -64°$ (5 min)→ −48° (10 min)→ −30° (2 h); $c = 2.0$, H_2O).

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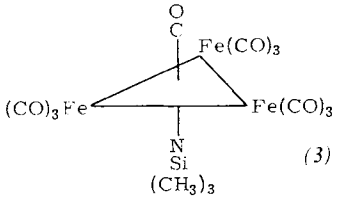
Fixation of Trimethylsilylnitrene as μ_3-Trimethylsilylimido(decacarbonyltriiron)

By *Ernst Koerner von Gustorf* and *Rosemarie Wagner*[*]

Trimethylsilyl azide[1] *(1)* exhibits a remarkably higher degree of thermal stability (b.p.$_{760}$ = 95 °C) than organic azides, due to $d_\pi - p_\pi$ interactions[2] between silicon and nitrogen. A similar stabilization is to be expected for trimethylsilylnitrene *(2)* formed from *(1)* by N_2 elimination. Very little has been reported hitherto about the chemistry of *(2)*[3]. In connection with investigations on the stabilization of labile intermediates in transition metal complexes[4] we have tried to trap *(2)* as a carbonyliron complex during the decomposition of *(1)*.

Like organic azides[5], *(1)* already decomposes at room temperature in the presence of $Fe_2(CO)_9$; $(CH_3)_3SiN[Fe_3(CO)_{10}]$ *(3)* is formed as brownish-red needles which decompose without melting at 110 °C. The mass spectrum of *(3)* shows, in addition to the molecular ion, fragments which correspond to successive loss of 10 CO groups. The ^{1}H-NMR spectrum (in benzene) contains a singlet due to a $(CH_3)_3Si$ group at 9.57 τ, which is shifted only slightly downfield compared to that of *(1)* (9.89 τ). In the IR spectrum (in *n*-hexane), which contains relatively few bands, five stretching vibrations of terminal CO groups are to be found (in order of decreasing intensity) at 2048, 2019.5, 2014, 1993, and 2088 cm^{-1}. An intense band at 1743 cm^{-1} is due to bridging CO[6, 7]. The symmetrical CH_3 bending vibration of the $(CH_3)_3Si$ group in *(3)*, like that in *(1)*, appears at 1255 cm^{-1} (in CCl_4).

The data obtained for *(3)* are consistent with formulation as a trimethylsilylnitrene-$[Fe_3(CO)_{10}]$ complex. Comparison with the known organonitrene complexes of similar configuration, $(CH_3N)_2[Fe_3(CO)_9]$[8] and $C_4H_9N[\pi\text{-}C_5H_5Ni]_3$[9] suggests *(3)* as having the structure proposed below. The trimethylsilylnitrene functions as a 4-electron donor, giving a "closed shell" complex.



(3)

X-ray structural analysis[10] confirms the almost perfect symmetrical arrangement of the $(CH_3)_3SiN$ group in *(3)* and shows that the axial CO group is triply bridging, in analogy to $[Fe_4(CO)_{13}]^{2-}$[11].

Hitherto it has not been possible to obtain *(3)* by photochemical reaction of $Fe(CO)_5$ with *(1)*. We are currently investigating the protolytic cleavage of the $(CH_3)_3Si$ group, which should lead to a complex of the imine.

Experimental:

A mixture of *(1)* (0.087 mol) and $Fe_2(CO)_9$ (0.028 mol) in benzene (70 ml) is mechanically stirred under argon for 24 h at 20 °C. Approximately 0.01 mol of gas is evolved. Unchanged $Fe_2(CO)_9$ is filtered off. The residue remaining after removal of solvent by evaporation is extracted with pentane. On cooling the extract to −78 °C, *(3)* crystallizes out; repeated recrystallization from pentane affords 0.8 mmol of analytically pure *(3)*[12].

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[7] An alternative assigument of this band as a CO stretching vibration in complexed $(CH_3)_3Si{-}N{=}C{=}O$ or $(CH_3)_3Si{-}CO{-}N<$ (both ligands could be formed by reaction of *(2)* with CO) can be ruled out since, in this case, *(3)* would have to be coordinatively unsaturated —which is not compatible with its properties.

[8] *R. J. Doedens*, Inorg. Chem. *8*, 570 (1969).

[9] *S. Otsuka*, *A. Nakamura*, and *T. Yoshida*, Inorg. Chem. *7*, 261 (1968); Liebigs Ann. Chem. *719*, 54 (1968).

[10] *B. L. Barnett* and *C. Krüger*, Angew. Chem. *83*, 969 (1971); Angew. Chem. internat. Edit. *10*, 910 (1971).

[11] *R. J. Doedens* and *L. F. Dahl*, J. Amer. Chem. Soc. *88*, 4847 (1966).

[12] $(CH_3)_3SiN[Fe_3(CO)_{10}]$: the composition has been confirmed by a complete elemental analysis. Mol.wt. (cryosopic in benzene) 538, calc. 535.

μ_3-Trimethylsilylimido-μ_3-carbonyltris-(tricarbonyliron)—Crystal and Molecular Structure

By *Bobby L. Barnett* and *Carl Krüger*[*]

μ_3-Trimethylsilylimido-μ_3-carbonyltris(tricarbonyliron) *(1)*, a product obtained on reaction of $(CH_3)_3SiN_3$ with $Fe_2(CO)_9$[1], crystallizes from pentane in the acentric space group $Pca2_1$ along [001] of the orthorhombic system. The unit cell ($a = 12.853$, $b = 13.316$, $c = 11.488$ Å), with a calculated density of 1.807 g/cm^3, contains four molecules of the title compound.

The molecular structure was determined from 1639 diffraction data by the heavy atom method. The positions of the iron atoms were deduced from a sharpened three-dimensional Patterson function; the light-atom positions were obtained by subsequent Fourier synthesis. Anisotropic least-squares refinement, in which the anomalous scattering of the Fe and Si atoms was included[2], gave a final $R = 4.3\%$.

The structure of *(1)* (Fig. 1) can be described by a pseudo-C_3 symmetry of the molecular skeleton including a triply coordinated carbonyl group on the iron cluster as well as a trimethylsilylimino group. The coordination of the equidistant Fe atoms is characterized by distorted octahedra in which three carbonyl groups (C_2,C_5,C_8) are slightly twisted out of the plane of the Fe atoms (see Fig. 2). The average Fe—C and C—O bond lengths are 1.798 and 1.141 Å, respectively, and correspond to analogous carbonyl-iron clusters; the same is true of the average Fe—Fe bond lengths of 2.535 ± 0.002 Å. The linearity of the carbonyl groups should be noted.

The bond lengths and angles in the symmetrically bound, triply bridging carbonyl groups C_{10}—O_{10} (see Fig. 3)

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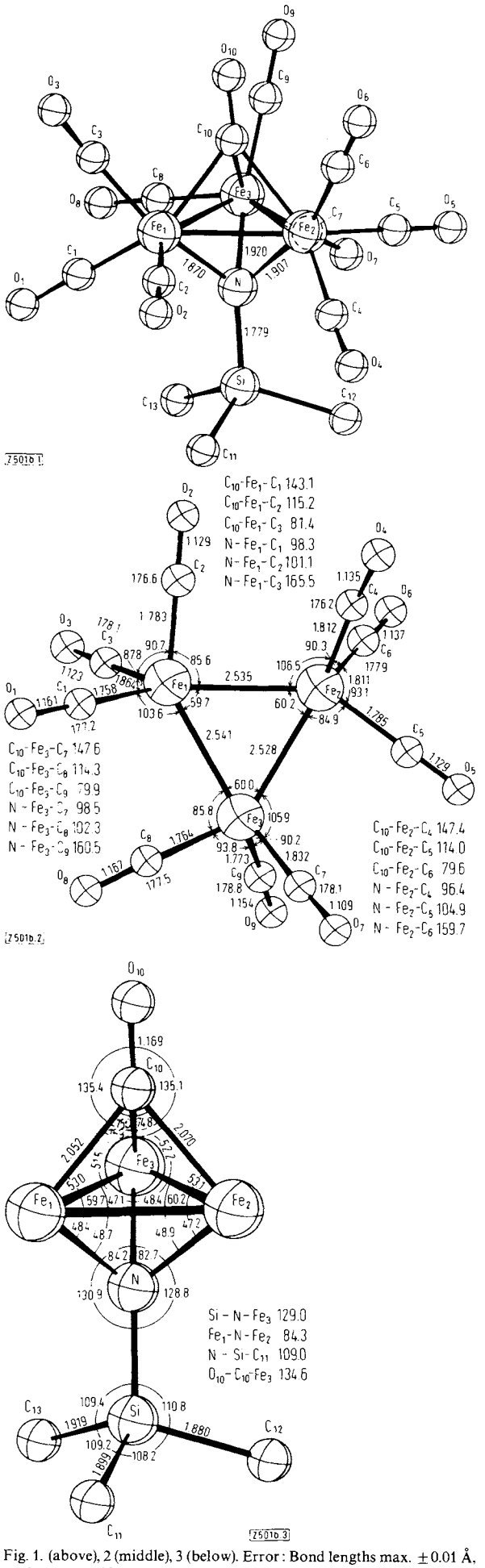


Fig. 1. (above), 2 (middle), 3 (below). Error: Bond lengths max. ±0.01 Å, angles max. ±1°.

correspond to those in the $[Fe_4(CO)_{13}]^{2-}$ grouping[3]. The vertical distance of the carbonyl C atoms from the Fe_1—Fe_2—Fe_3 plane is 1.466 Å, that of the N atoms 1.209 Å. The N—Fe bond lengths (see Fig. 1) are not identical and thus reflect a slight asymmetry of the molecule. The average Fe—N bond length (1.899 Å) is shorter than that in doubly bridged imidoiron compounds (1.94 to 2.00 Å)[4]; the angles at the N atoms, however, are on average 4° greater and approximate ideal tetrahedral angles. The value found for the Si—N bond length can readily be explained as due to decreased (p→d) π interaction causing some lengthening of the bond.

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German version: Angew. Chem. *83*, 969 (1971)

[1] *E. Koerner von Gustorf* and *R. Wagner*, Angew. Chem. *83*, 968 (1971); Angew. Chem. internat. Edit. *10*, 910 (1971).

[2] All calculations and drawings were carried out on a PDP-10 time-sharing computer. A list of the structure factors is available from the authors (C. K.).

[3] *R. J. Doedens* and *L. F. Dahl*, J. Amer. Chem. Soc. *88*, 4847 (1966); *D. C. Bradley, M. B. Hursthouse* and *P. F. Rodesiler*, Chem. Commun. *(1969)* 14; *H. Hess*, Acta Crystallogr. *B 25*, 2342 (1969).

[4] *R. J. Doedens*, Inorg. Chem. *8*, 570 (1969).

Electrocyclic Reactions of Radicals[**]

By *Gernot Boche* and *Günter Szeimies*[*]

We have found that the avoidance of crossing resulting from loss of symmetry allows the electrocyclic reaction of radicals to proceed *via* a "symmetry-controlled" activation barrier to the ground state of the product.

The first treatment of electrocyclic radical reactions from the standpoint of conservation of orbital symmetry[1] is due to *Woodward* and *Hoffmann*[2]. Their frontier orbital approach predicts that the stereochemical course of these reactions should be controlled by the symmetry of the highest singly occupied molecular orbital of the polyene reactant.

Shortly afterwards, *Longuet-Higgins* and *Abrahamson*[3] published orbital and state correlation diagrams for the interconversion of cyclopropyl and allyl radical which showed this isomerization to be symmetry-forbidden, whether by a disrotatory or a conrotatory process; the ground states of the reactants and products both belong to different symmetry classes and in order to conserve orbital symmetry the thermal reaction would thus always have to give an electronically excited state of the product. These authors therefore expected a "much higher activation energy" for thermal ring opening of the cyclopropyl radical than for isomerization of the cyclopropyl cation or anion.

The above argument should be capable of generalization: This would mean that all thermal electrocyclic reactions of radicals, radical cations, and radical anions are "symmetry forbidden" and require a large activation energy (Figs. 1 and 2).

This prediction cannot be confirmed experimentally. On the contrary, the activation energy of cyclopropyl radical ring opening in the gas phase is about 20—22 kcal/mol[4] and for some substituted cyclopropyl radicals[5] it is

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lowered to such an extent that, even in cumene, ring opening competes successfully with H abstraction[6].

Disrotatory ring opening to give the homocyclooctatetraene radical anion on reaction of *cis*-bicyclo[6.1.0]nona-2,4,6-triene with alkali metals, although apparently symmetry-forbidden too[1], actually occurs at as low a temperature as $-80\,^{\circ}C$[7].

Judging by the relatively low activation energies, it seems extremely unlikely that these radical reactions should lead to an electronically excited state of the product.

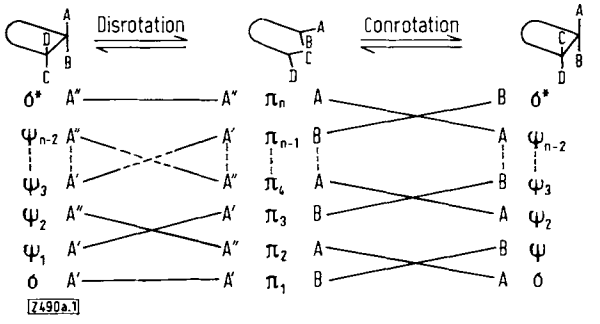


Fig. 1. Orbital correlation diagram for the disrotatory and the conrotatory ring closure of a linear conjugated π-electron system.

Perturbation by substitution, non-symmetrical molecular vibrations, or not fully concerted changes in the geometrical parameters during reaction can lead to a lowering or to a complete anullment of the symmetry of a reacting molecule. This should have no significant effect, however, on the validity of the rules for the conservation of orbital symmetry[1] for closed shell systems.

A different situation prevails in electrocyclic interconversions of radicals. The destruction of the symmetry elements common to reactants and products, C_2 (conrotation) and σ_v (disrotation), leads in the course of the reaction to an increasing interaction between the configurations A and B, or A′ and A″, of the unperturbed molecule[8], shown as crossing in Figure 2. The magnitude of this interaction will

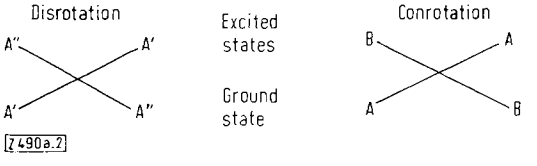


Fig. 2. State correlation diagram for the disrotatory and for the conrotatory electrocyclic radical reaction with conservation of orbital symmetry (in general form).

depend upon the degree of perturbation and the energy difference between the two states[9]. Since the energies of the two states approach each other very closely along the reaction coordinate, even a slight distortion of the reacting system suffices for a significant interaction, which in turn obviates the need for crossing (noncrossing rule) and affects the correlation between the ground states.

The electrocyclic reaction of radicals thus leads, owing to the crossing which is laid down at the start of the reaction but later avoided by loss of symmetry, *via* a "symmetry-controlled" activation energy barrier[10] to the ground state of the product (Fig. 3).

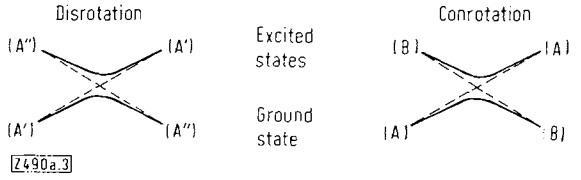


Fig. 3. Realistic course (——) of the correlation lines in electrocyclic radical reactions (in general form).

The activation energy of a disrotatory or conrotatory electrocyclic radical reaction is therefore difficult to estimate even qualitatively[11]. It should depend upon the energy of the electronic ground state and the excited states of the reacting system and also upon the degree of symmetry perturbation along the reaction coordinate. A quantitative treatment of the cyclopropyl-allyl radical interconversion with the aid of semiempirical SCF MO methods is given in the following communication[12].

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[1] For a review see *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[2] *R. B. Woodward* and *R. Hoffmann*, J. Amer. Chem. Soc. *87*, 395 (1965).

[3] *H. C. Longuet-Higgins* and *E. W. Abrahamson*, J. Amer. Chem. Soc. *87*, 2045 (1965).

[4] *G. Greig* and *J. C. J. Thynne*, Trans. Faraday Soc. *62*, 3338 (1966); *63*, 1369 (1967).

[5] *G. Wittig*, *V. Rautenstrauch*, and *F. Wingler*, Tetrahedron Suppl. *7*, 189 (1965); *H. M. Walborsky* and *J. C. Chen*, J. Amer. Chem. Soc. *92*, 7573 (1970).

[6] The activation energy for H abstraction by cyclopropyl radicals should lie between 7 and 8 kcal/mol; *G. Greig* and *J. C. J. Thynne*, Trans. Faraday Soc. *63*, 2196 (1967).

[7] *R. Rieke*, *M. Ogliaruso*, *R. McClung*, and *S. Winstein*, J. Amer. Chem. Soc. *88*, 4729 (1966); *T. J. Katz* and *C. Talcott*, *ibid.* *88*, 4732 (1966).

[8] A similar mechanism is responsible for the occurrence of symmetry-forbidden transitions in electronic spectra.

[9] See, *e.g.*, *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969, pp. 47 ff.

[10] It is worthwhile mentioning that in contrast to "symmetry-forbidden" electrocyclic transformations of closed shell systems, only *one* electron instead of two has to follow an energetically unfavorable pathway.

[11] *K. Fukui*, Accounts Chem. Res. *4*, 57 (1971). The Evans Principle, another qualitative method for the treatment of electrocyclic reactions (see *M. J. S. Dewar*, Tetrahedron Suppl. *8*, 75 (1966)), is not applicable to radicals.

[12] *G. Szeimies* and *G. Boche*, Angew. Chem. *83*, 979 (1971); Angew. Chem. internat. Edit. *10*, 912 (1971).

Electrocyclic Transformation of Cyclopropyl Radical into Allyl Radical: A Semiempirical SCF MO Study[**]

By *Günter Szeimies* and *Gernot Boche*[*]

All electrocyclic rearrangements of radicals should pass over a symmetry-controlled activation barrier[1]. Since qualitative considerations permit no unequivocal predictions to be made concerning the chemically interesting

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problem of the activation energies of the disrotatory and the conrotatory ring opening process[1] we have performed semiempirical SCF MO calculations on the cyclopropyl-allyl radical rearrangement by the CNDO/2[2] and MINDO/2 techniques[3].

The geometry of the cyclopropyl radical was taken to correspond to that of cyclopropane[4] and we assumed a unidimensional reaction coordinate for the ring opening, *i.e.* all geometric parameters involved in the transformation were transformed continuously into those of the allyl system[5]. C—H bond lengths remained unchanged. Energies were calculated for the cyclopropyl and allyl radicals as well as nine geometric intermediates, corresponding to an opening of the $C^2C^1C^3$ angle from 60° to 120° in steps of 6°.

Since the cyclopropyl radical probably has an inversion barrier at the radical center[6], the tricovalent carbon atom thus assuming a pyramidal structure, two disrotatory ring opening modes are possible. H^1 and H^3 (see Fig. 1) can either approach (disrotation 1) or move away from each other (disrotation 2). There is only one possible conrotatory mode.

The reaction course assumed has the C_2 axis or the σ_v plane as symmetry element along the reaction coordinate[***]. The computation methods chosen take account only of the ground state configuration; the increase or decrease in energy takes place on correlation pathways of different state symmetry (A′ and A″ for disrotation, and A and B for conrotation). The point of intersection characterizes the activated complex and thus allows the calculation of the activation energy. This model reaction is "symmetry forbidden", as is also apparent from the results of the calculation. The CNDO/2 bond indices[7] of the C—C bonds exhibit sharp discontinuities in the region of the activated complex.

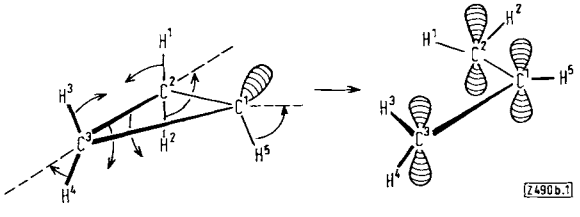


Fig. 1. Movement of the H atoms during disrotation 1.

We have already pointed out[1] that a perturbation of the symmetry along the reaction coordinate could energetically favor the reaction as a result of configurational interaction. With this in mind, our calculations can be seen to give an upper limit for the activation energy of the cyclopropyl-allyl radical transformation (Table 1). Figure 2 shows the variation in energy along the reaction coordinate for the MINDO/2 case.

CNDO/2 and MINDO/2 give very similar results. However, we regard the MINDO/2 values as more reliable since the underestimation of ring strain effects is less serious than by CNDO/2.

The value of 20—22 kcal/mol[9] determined by *Grey* and *Thynne* for the ring opening of the cyclopropyl radical is in good agreement with the calculated figures. That the activation energy can be even lower for suitably substituted cyclopropyl radicals is clear from the successful competition of ring opening with H abstraction[10], whose activation energy is only 7—8 kcal/mol[11].

[***] Strictly speaking this applies to the conrotation only when the reaction is made to start with a trigonal radical center.

Table 1. Calculated activation energies (kcal/mol) for the ring opening of cyclopropyl radical to give allyl radical. In the case of MINDO/2 the ring strain in the parametrization used is estimated as about 12 kcal/mol too low [3, 8]. The values in parentheses take this into consideration.

Method	Disrotation 1	Disrotation 2	Conrotation
CNDO/2	31.8	42.5	40.7
MINDO/2	30.1	46.6	37.5
	(18.1)	(34.6)	(25.5)

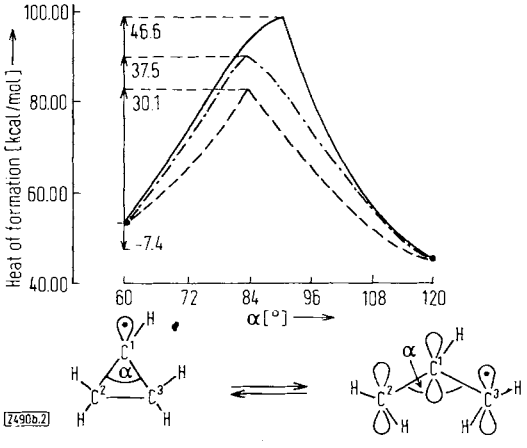


Fig. 2. Energetic course of cyclopropyl-allyl radical transformation, calculated by MINDO/2. – – –: disrotation 1; ———: disrotation 2; –·–·–: conrotation.

[1] *G. Boche* and *G. Szeimies*, Angew. Chem. *83*, 978 (1971); Angew. Chem. internat. Edit. *10*, 911 (1971).

[2] *J. A. Pople, D. P. Santry*, and *G. A. Segal*, J. Chem. Phys. *43 S*, 129 (1965); *J. A. Pople* and *G. A. Segal, ibid. 44*, 3289 (1966); for parameters see *K. B. Wiberg*, J. Amer. Chem. Soc. *90*, 59 (1968).

[3] *N. C. Baird* and *M. J. S. Dewar*, J. Chem. Phys. *50*, 1262 (1969); for parameters see *N. Bodor, M. J. S. Dewar, A. Harget*, and *E. Haselbach*, J. Amer. Chem. Soc. *92*, 3854 (1970).

[4] *L. E. Sutton*: Tables of Interatomic Distances and Configurations in Molecules and Ions. Spec. Publ. No. 11, Chem. Soc. London 1958, Suppl. Spec. Publ. No. 18, 1965.

[5] *D. T. Clark* and *G. Smale*, Tetrahedron *25*, 13 (1969).

[6] *M. J. S. Dewar* and *J. M. Harris*, J. Amer. Chem. Soc. *91*, 3652 (1969); *M. J. S. Dewar* and *M. Shanshal, ibid. 91*, 3654 (1969), and further literature cited there.

[7] *K. B. Wiberg*, Tetrahedron *24*, 1083 (1968); *C. Trindle* and *O. Sinanoglu*, J. Amer. Chem. Soc. *91*, 853 (1969).

[8] *M. J. S. Dewar, E. Haselbach*, and *M. Shanshal*, J. Amer. Chem. Soc. *92*, 3505 (1970).

[9] *G. Greig* and *J. C. J. Thynne*, Trans. Faraday Soc. *62*, 3338 (1966); *63*, 1369 (1967); the stereochemistry of ring opening is unknown.

[10] *G. Wittig, N. Rautenstrauch*, and *F. Wingler*, Tetrahedron Suppl. *7*, 189 (1965); *H. M. Walborsky* and *J. C. Chen*, J. Amer. Chem. Soc. *92*, 7573 (1970).

[11] *G. Greig* and *J. C. J. Thynne*, Trans. Faraday Soc. *63*, 2196 (1967).

[12] *R. B. Woodward* and *R. Hoffmann*, J. Amer. Chem. Soc. *87*, 395 (1965), *H. C. Longuet-Higgins* and *E. W. Abrahamson*, J. Amer. Chem. Soc. *87*, 2045 (1965).

[13] The observation that reaction of *syn*-9-chloro(or methoxy)-*cis*-bicyclo[6.1.0]nona-2,4,6-triene with alkali metal leads to all-*cis*-cyclononatetraenyl anion by disrotatory ring opening, could be regarded as an example. The corresponding *anti* compounds, on the other hand, give mainly *trans,cis,cis,cis*-cyclononatetraenyl anion; *G. Boche* and *D. Martens*, unpublished; *G. Boche, D. Martens*, and *W. Danzer*, Angew. Chem. *87*, 1003 (1969); Angew. Chem. internat. Edit. *8*, 984 (1969).

[14] *M. S. Gordon*, J. Amer. Chem. Soc. *91*, 3122 (1969).

Both CNDO/2 and MINDO/2 indicate a definite preference among the possible modes of ring opening: Contrary to earlier qualitative predictions[12], our results show that disrotation 1 should require the lowest activation energy[13].

Why is this reaction path more favorable than the others? The calculated total energies can be resolved into interpretable energy components[14]. Analysis of these CNDO partial energies shows that the differences in the activation energies lie almost exclusively in the term that is decisive for covalent bonding ($\sum\sum_{A<B} E^1_{AB}$, for notation see ref. [14]). Further dissection of the summation term indicates that the activation energy difference is due mainly to the contributions of the three C—C bonds. In the case of disrotation 1 the carbon centers in the transition state exhibit more pronounced mutual covalent bonding than in conrotation or disrotation 2.

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Representation of Chemical Systems and Interconversions by *be* Matrices and Their Transformation Properties[1]

By *Ivar Ugi* and *Paul Gillespie*[*]

Isoelectronic chemical entities that contain the same atomic nuclei are described by the same Schrödinger equation. These include not only families of isomeric molecules but *families of isomeric ensembles of molecules* (FIEM) as well.

The latter concept arises as an extension of the isomerism equivalence relation[2] of individual molecules to ensembles of molecules (EM). EM belonging to the same FIEM originate from the same set $\boldsymbol{A}$ of atoms.

The C_3H_8O FIEM contains, *e.g.*, $EM_0=\{3C+8H+2O\}$,
$EM_1=\{CH_3—CHOH—CH_2OH\}$,
$EM_2=\{CH_3—CH_2—CHO+H_2O\}$,
$EM_3=\{CH_3CHO+CH_3OH\}$,
$EM_4=\{CH_2O+CH_3—CH_2OH\}$,
$EM_5=\{CH_3—CH{=}CH_2+H_2O_2\}$, and
$EM_6=\{CH_3—CH_2—CH_3+O_2\}$, *etc.*

Distinguishable IEM of a FIEM (we treat stereoisomers as being equivalent here) can be represented by a family of *be* matrices $\boldsymbol{F}=(\boldsymbol{M}_0,\boldsymbol{M}_1,\ldots,\boldsymbol{M}_\phi,\ldots\boldsymbol{M}_f)$. In general the number $f\leqslant(2N)!/2^T\,(2N-T)!$ or $f\leqslant N!/(N-T/2)!$, if no EM with unpaired electrons are considered. N is the sum of the AO's and LCAO's occupied in the ground states of the IEM by the $T=T_0$ valence electrons of $\boldsymbol{A}$. The *be* matrix $\boldsymbol{M}_\phi$ of an EM_ϕ consisting of a set $\boldsymbol{A}$ containing n atoms, $\boldsymbol{A}=\{A_1,A_2,\ldots A_n\}$ is an $n\times n$ matrix (eq. (1))[3].

$$\boldsymbol{M}_\phi=\begin{bmatrix} e_1 & i_{12} & i_{13} & i_{14}\cdots i_{1n} \\ b_{21} & e_2 & i_{23} & i_{24}\cdots i_{2n} \\ b_{31} & b_{32} & e_3 & i_{34}\cdots i_{3n} \\ b_{41} & b_{42} & b_{43} & e_4\cdots i_{4n} \\ \vdots & \vdots & \vdots & \vdots \\ b_{n1} & b_{n2} & \cdots & e_n \end{bmatrix} \quad (1)$$

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The entries $b_{\mu\nu}$ of the *b*-region (lower triangle) where $\mu>\nu$ are the formal bond orders of the bonds between pairs of atoms A_μ and A_ν. Off diagonal matrix elements $b_{\mu\nu}$ may be simply interpreted as follows:

$b_{\mu\nu}=0$: no formal bond between A_μ and A_ν
$b_{\mu\nu}=1$: $A_\mu-A_\nu$ (= single bond)
$b_{\mu\nu}=2$: $A_\mu=A_\nu$ (= double bond)
$b_{\mu\nu}=3$: $A_\mu\equiv A_\nu$ (= triple bond)

Fractional bond orders must be employed for representations of multi-center bonds. For third and higher row elements $b_{\mu\nu}>1$ is usually avoided. Since the chemical bond is a symmetrical relation $b_{\mu\nu}=b_{\nu\mu}$, it suffices to use the *b*-region for bond information freeing the upper triangle (*i*-region, see Ref.[7]) for any form of additional information on the EM_ϕ. The matrix elements $i_{\mu\nu}$ of the *i*-region can represent any property, *e.g.*, thermodynamic, kinetic, electronic, steric[4], *etc.*, that exists between pairs of atoms A_μ and A_ν, unless a symmetrical matrix is preferred because of advantages upon transformation[**].

Diagonal matrix elements $e_{\lambda=\mu\mu=\nu\nu}$ (eq. (2)) are numerically equivalent to the number of valence electrons belonging to atom A_λ in EM_ϕ, *i.e.*, the electrons in the σ and π bonds by which A_λ is connected to other atoms and e'_λ, the "free" valence electrons of A_λ[**].

$$\bar{e}_\lambda=\sum_{\nu=1}^{\nu=\lambda-1} b_{\lambda\nu}+\sum_{\mu=\lambda+1}^{\mu=n} b_{\mu\lambda} \quad (2)$$

$$e_\lambda=e'_\lambda+\bar{e}_\lambda \quad (2a)$$

$$T=\sum_1^n e_\lambda \quad (3)$$

$$T_0=\sum_1^n e'_{0\lambda} \quad (3a)$$

$$\hat{e}_\lambda=e'_\lambda+2\bar{e}_\lambda \quad (4)$$

$$\hat{e}_\lambda=\hat{e}_{\lambda,\mathrm{opt}} \quad (4a)$$

$$\hat{e}_{\lambda,\min}\leq\hat{e}_\lambda\leq\hat{e}_{\lambda,\max} \quad (4b)$$

$$e^+_\lambda=e'_{0\lambda}-e_\lambda \quad (5)$$

The numbers $\hat{e}_\lambda$ of valence electrons that surround A_λ have preferred values, *e.g.*, 8 for B to F, or lie within an interval defined by eq. (4b), characteristic of $A_{0\lambda}$. The limits, $\hat{e}_{\lambda,\min}$ and $\hat{e}_{\lambda,\max}$ are 0 and 2 for the elements of group IA of the periodic table, 0 and 4 for group IIA, 6 and 8 for second row elements B to F and 6 and 12 for third row elements Si to Cl.

The trace T, eq. (3), of the *be* matrix $\boldsymbol{M}_\phi$ in EM_ϕ is equal to T_0, eq. (3a), the sum of all valence electrons for each of the atoms $A_1,\ldots A_m$ that belong to $\boldsymbol{A}$. The diagonal entries $e'_{0\lambda}$ of $\boldsymbol{M}_0$ are the numbers of valence electrons of the elements $A_{0\lambda}$ to which the A_λ belong; *e.g.*, ${}_He'_{0\lambda}=1$, ${}_Ce'_{0\lambda}=4$, ${}_Ne'_{0\lambda}=5$, ${}_Oe'_{0\lambda}=6$, *etc.*

The formal net electrical charge, e^+_λ, of an atom A_λ is given by eq. (5); here $e'_{0\lambda}$ represents the positive core charge.

In addition to the selection rule defined by eq. (4) further selection rules may be based upon preferred coordination numbers for the various elements within $\boldsymbol{A}$.

[**] Note added in proof: Sometimes it is advantageous to represent the EM by symmetric *be*-matrices in which the numbers of free valence electrons e'_λ are entered on the diagonal. In this case, the sums over the rows or columns correspond to the e_λ and the sums over all entries correspond to the total number $T=T_0$ of valence electrons.

Symmetries and/or permutational equivalencies[2, 5] in the EM∈FIEM may be represented by permutations of the indices λ or μ and ν, respectively.

be-Matrices which differ only by permutations of indices whose atoms belong to the same element are equivalent. Any set of equivalent ***be***-matrices contains ε! irreducible matrices. These are in block form if the represented EM contains ε disjoint molecules. Further, they are the ***be***-matrices of the individual molecules within the EM. Equivalent irreducible ***be***-matrices differ only by permutations of the blocks.

Chemical processes correspond to interconversions $EM_\phi \rightarrow EM_\psi$ of IEM (EM_ϕ and $EM_\psi \in FIEM$) and are represented by eq. (6) where R_ρ is a transformation operator.

$$M_\psi = R_\rho \cdot M_\phi \tag{6}$$

The set A_0 of free atoms $A_0 = \{A_{01}, A_{02}, \ldots A_{0n}\}$ is represented by a ***be*** matrix M_0 whose diagonal elements are $e'_{0\lambda}$, and whose *b*-region contains only zeros. Transformations R_ρ generate from M_0, according to eq. (6), the set $\boldsymbol{F}$ that corresponds to the total FIEM[6]. Cycles of such transformations form closed lines in the corresponding topological space.

Equation (6) then may be considered the consequent result of the application of logical structures[5] to chemical systems, in short, a master equation for describing the chemistry of the FIEM.

The various operators R_ρ correspond to various types of chemical processes.

It is interesting to note that eq. (6) contains any of the conservation laws one normally assumes in the solution to problems within chemical systems, *e.g.*, conservations of mass, charge, electrons, *etc.* It follows that those transformations generated as a result of the operation of R_ρ acting on some M_ϕ correspond to processes described by a time-dependent Schrödinger equation.

Potential applications of this equation include the computer assisted planning of syntheses, elucidation of reaction mechanisms and mass spectrometric patterns[7], and documentation of chemical reactions.

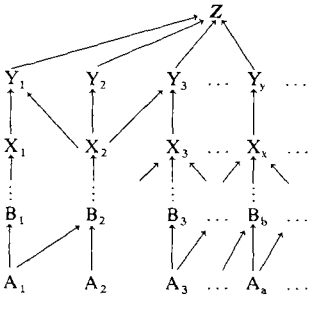
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Matter Preserving Synthetic Pathways and Semi-Empirical Computer Assisted Planning of Syntheses[1]

By *Ivar Ugi* and *Paul Gillespie*[*]

Synthetic planning processes consist of two steps; first one looks for the pathways that lead from readily available starting materials to a target molecule ***Z***, then one decides which of these conceivable pathways is the optimum as a function of some chosen criteria. This communication deals primarily with the problem of determining the available synthetic alternatives without detailed discussion of the evaluation problem[3].

The search for a synthetic pathway is best accomplished by "working the problem backwards"[4]. A target molecular structure ***Z*** is analyzed for "seams" in order to find the set ***Y*** of precursors $\{Y_1, Y_2, \ldots, Y_y, \ldots\}$ that can be converted by one step reactions into ***Z***. A set ***X*** of compounds $\{X_1, X_2, \ldots, X_x, \ldots\}$ are then sought which can be converted in one-step reactions into the precursors $\{Y_1, Y_2, \ldots, Y_y, \ldots\}$ until a set ***A*** of convenient starting materials $\{A_1, \ldots, A_a, \ldots\}$ is achieved. Thus the mappings $A_a \rightarrow B_b \rightarrow \cdots \rightarrow Z$ yields a tree (1) of synthetic pathways.



(1)

An existing computer program[5], designed to produce this "tree", and employing empirical information concerning known synthetic reactions, is limited to the generation of those synthetic pathways which are suggested to the chemist by his knowledge of the literature.

As in all chemical processes, synthetically useful reactions including sequences of reactions (if suitably defined) proceed with a constant matter balance[6] and correspond to interconversions of IEM∈FIEM[2]. Therefore, eq. (2)[2]

$$M_\psi = R_\rho \cdot M_\phi \tag{2}$$

provides the basis for a program conceptually dependent upon fundamental principles which, in contrast to the

[1] Chemistry and Logical Structures, Part 3.—Part 2: see Ref. [2].

[2] *P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis,* and *I. Ugi*, Angew. Chem. *83*, 691 (1971); Angew. Chem. internat. Edit. *10*, 687 (1971).

[3] The ***be*** matrices differ fundamentally from extended connectivity matrices, the so-called principal matrices of molecules, by being endowed with well defined transformation properties. Further, the ***be*** matrices not only refer to molecules but EM as well.

[4] The steric features of the considered systems can also be represented by additional diagonal entries referring to the local configurations of the vicinities of the individual atoms; the numbering of the atoms can serve as a sequence rule for descriptors[5]. An alternative would be to include some suitably chosen nuclear coordinates, *e.g.* cartesian or approximate cubic lattice coordinates[5].

[5] *I. Ugi, D. Marquarding, H. Klusacek, G. Gokel,* and *P. Gillespie*, Angew. Chem. *82*, 741 (1970); Angew. Chem. Internat. Edit. *9*, 703 (1970).

[6] We gratefully acknowledge a valuable discussion with Prof. *J. Dugundji* (Department of Mathematics, U.S.C) during which the following evolved: The *be*-matrices of an FIEM define a finite metric space which may be properly called the EM space or the chemical topology of the FIEM. In this space the distance *d* between two points (*i.e.*, EM and EM', represented by their *be*-matrices *M* and *M'*) is given by $d = |M - M'|$. The EM space of a FIEM is a *subspace* of the *universal chemical topology* referring to the universal FIEM that contains all chemical compounds of the universe. Chemical topology, as a term, has previously been used in an attempt to represent steric features of molecules topologically[5]. It follows that a synthetic route is a pathway in the topological space of an FIEM connecting a starting material point, frequently *via* other points, with that of a product such that none of the distances between two points exceeds a specified limit (see Ref. [7]).

[7] *I. Ugi* and *P. Gillespie*, Angew. Chem. *83*, 982 (1971); Angew. Chem. internat. Edit. *10*, 915 (1971).

[*] Prof. Dr. I. Ugi and Dr. P. Gillespie
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above empirical, analogy oriented program, generates the complete set of all conceivable synthetic routes for a given target. This includes new reactions, *i.e.*, computer invented pathways suggesting experimental discovery.

At any given moment, these synthetic pathways not only contain the characteristic intermediates $A_a, B_b, \ldots Y_y, \boldsymbol{Z}$, but all unconsumed starting materials and existing by-products that accompany the intermediates as well. The pathway $A_a \rightarrow B_b \rightarrow \cdots \boldsymbol{Z}$ shown in scheme (3) may also be

$$\begin{array}{lll} A_a + A'_a & \rightarrow & B_b + B''_b \\ B_b + B'_b & \rightarrow & C_c + C''_c \\ C_c + C'_c & \rightarrow & \cdots \\ \cdots & \rightarrow & \cdots \\ \cdots & \rightarrow & X_x + X''_x \\ X_x + X'_x & \rightarrow & Y_y + Y''_y \\ Y_y + Y'_y & \rightarrow & \boldsymbol{Z} + Z'' \end{array} \qquad (3)$$

represented by the balance of matter preserving pathway $EM_{initial} \rightarrow EM_b \rightarrow \cdots EM_y \rightarrow EM_{final}$ (4), with $A_a \in EM_{initial}$, $B_b \in EM_b, \ldots, \boldsymbol{Z} \in EM_{final}$.

$$\begin{array}{lll} EM_{initial} & = & \{A_a + A'_a + B'_b + C'_c + \cdots + X'_x + Y'_y\} \\ EM_b & = & \{B_b + B''_b + B'_b + C'_c + \cdots + X'_x + Y'_y\} \\ EM_c & = & \{B_b + B''_b + C'_c + \cdots + X'_x + Y'_y\} \\ \vdots & & \vdots \\ EM_x & = & \{B''_b + C''_c + \cdots + X_x + X''_x + X'_x + Y'_y\} \\ EM_y & = & \{B''_b + C''_c + \cdots + X''_x + Y_y + Y''_y + Y'_y\} \\ EM_{final} & = & \{B''_b + C''_c + \cdots + X''_x + Y''_y + \boldsymbol{Z}_z + Z''_z\} \end{array} \qquad (4)$$

An input of M_{final} is required for the matter preserving synthetic path computer program. Additional input of $M_{initial}$, if known, reduces output as well as run time. From these inputs, *i.e.* ***be***-matrices[2], the complete set of transformations, $R_z, \ldots R_a$, for

$$M_{final} = R_z \cdot R_y \cdot, \ldots R_b \cdot R_a \cdot M_{initial} = \bar{R} \cdot M_{initial} \qquad (5)$$

is generated. Sequential application of the operators $R_a, \ldots, R_z$ on $M_{initial}$ yield the ***be*** matrices which represent the EM_ϕ encountered on the individual paths while the operators R_ρ represent the chemical processes of the synthetic steps.

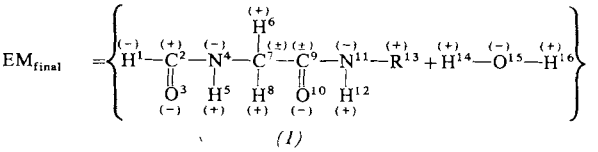
If it is not possible to derive the EM_{final} directly from the formula of $\boldsymbol{Z}$, one adds, as the required complements, α molecules of A—B, equivalent to $A^\oplus + :B^\ominus$ or $A\cdot + B\cdot$, and β molecules of C=D representing unsaturated by-products (*e.g.*, $(C_6H_5)_3P{=}O$) of synthetic steps to form the $EM_{final} = \{\boldsymbol{Z} + \alpha(A{-}B) + \beta(C{=}D)\}$. From this the program yields EM_y representations containing the Y_y that can be identified, simultaneously identifying the complements A—B and C=D of $\boldsymbol{Z}$. In the next step the Y_y are subjected to an analogous treatment *etc.*, until readily available starting materials are reached.

Simplification of matrices with an attendent reduction of computer time can be gained by replacing a substituent on $\boldsymbol{Z}$ with an R$^\cdot$ ($0 \leq_R \hat{e}_\lambda \leq 2, {}_R e_{0\lambda} = 1$) symbol possessing an electron or its polyfunctional analog if this substituent appears in a starting material and no reaction sequence involves it.

In order to achieve a convenient and economical procedure the operator R_ρ must be subjected to *empirical selection rules* such that those steps can be avoided that do not proceed with practical rates or yields. The rules must provide that only those transformations are used that correspond to operations whereby one, two or in exceptional cases three connections are dissected or made, and bond orders $b_{\mu\nu}$ in M_ϕ are changed by $\Delta b_{\mu\nu} \pm 1$ with simultaneous changes in $\hat{e}_\lambda$ by $\Delta\hat{e}_\lambda = \pm 1$ (for radical reactions) or by $\Delta\hat{e}_\lambda = 0, \pm 2$ (for ionic reactions). Preferred transformations can be effected by loading the transformation invariant *i*-region of the ***be*** matrix[2] with further information regarding the system at hand, *e.g.*, kinetic or thermodynamic pair parameters. Relative "charge affinity" information in the form of an extended Evans-Lapworth Scheme may be used to indicate by the algebraic sign and values of the $i_{\mu\nu}$ which of the bonds $b_{\mu\nu}$ are preferentially subject to ionic reactions and determine which of the atoms (A_μ or A_ν) will play the nucleophilic role[7, 8]. Heats of bond formation $\Delta H_{\mu\nu}$ between A_μ and A_ν may be included as off diagonal matrix elements, $\Delta H_{\mu\nu}$, in the *i*-region of the ***be*** matrices. A summation of these $\Delta H_{\mu\nu}$ according to the *b*-region serves as an estimate of the heat of formation for the corresponding EM_ϕ. This information will allow the program to reject excessively endothermic reactions.

Subsequent selection rules based upon other known principles such as the Dewar-Evans rule[9–17] as well as general empirical or semi-empirical information on chemical reactivity can be added to the *i*-region of the ***be*** matrices. The latter include observations to the effect that in cyclic processes involving five- or six-membered rings and carbon compounds, those R_ρ are preferred that represent reactions involving multiple bonds, bonds immediate or next neighbors to multiple bonds or electrically charged or heteroatoms. If more than one of these conditions applies to one of the bonds the preference for reactions involving these bonds is enhanced.

An example of a synthetic planning process for *N*-formylglycine-*N'*-methylamide *(1)* may serve to illustrate the present method and its potential usefulness. If one looks for those syntheses of *(1)* that proceed with the loss of one mole of water, one starts with R = CH_3 and

$EM_{final} =$ 

(1)

assigns numbers to the atoms of *(1)* as indicated. Further, one can label the latter with (+) or (−) according to an Evans-Lapworth pattern[7, 8]. From these, one obtains a *bei* matrix M_{final} (6a). The *b*-region entries represent the bond system of EM_{final}; the number, $b_{32} = 2$, in the second column, third row means that in *(1)* the C-atom. 2 is connected by a double bond to the O-atom 3. Diagonal entries represent those numbers of electrons belonging to the corresponding atoms. For example, the third diagonal element from the top $e_3 = 2 + 4$ relates to the fact that six valence electrons belong to O-3 of which two are bonding and four are "free". Entries to the *i*-region[2] are relative "charge affinity" data concerning pairs of atoms in the sense of an extended Evans-Lapworth pattern; the (+) sign of $i_{24} = +2$ in (6a) indicates that C-atom 2 is electrophilic *vs.* N-atom 4, the latter being nucleophilic relative to the former. The value 2 of i_{24} represents a crude estimate of a relative charge affinity difference which does not always correspond to an electronegativity difference. Higher $i_{\mu\nu}$ values for a pair of atoms (A_μ,A_ν) indicates an increased likelihood for an ionic reaction involving bond making or bond breaking between A_μ and A_ν.

	H 1	C 2	O 3	N 4	H 5	H 6	C 7	H 8	C 9	O 10	N 11	H 12	R 13	H 14	O 15	H 16
H 1	*1*	−1	+3	+2	0	0	±1	0	±1	+3	+2	0	0	0	+3	0
C 2	1	*4*	+3	+2	0	0	0	0	0	+3	+2	0	0	0	+3	0
O 3	0	2	*2+4*	−1	−3	−3	−3	−3	−3	0	−1	−3	−3	−3	0	−3
N 4	0	1	0	*3+2*	−2	−2	−2	−2	−2	+1	0	−2	−2	−2	+1	−2
H 5	0	0	0	1	*1*	0	+1	0	±1	+3	+2	0	0	0	+3	0
H 6	0	0	0	0	0	*1*	+1	0	±1	+3	+2	0	0	0	+3	0
C 7	0	0	0	1	0	1	*4*	−1	±2	+3	+2	−1	−1	−1	+3	−1
H 8	0	0	0	0	0	0	1	*1*	±1	+3	+2	0	0	0	+3	0
C 9	0	0	0	0	0	0	1	0	*4*	+3	+2	0	0	0	+3	0
O 10	0	0	0	0	0	0	0	0	2	*2+4*	−1	−3	−3	−3	0	−3
N 11	0	0	0	0	0	0	0	0	1	0	*3+2*	−2	−1	−2	+1	−2
H 12	0	0	0	0	0	0	0	0	0	0	1	*1*	0	0	+3	0
R 13	0	0	0	0	0	0	0	0	0	0	1	0	*1*	0	+3	0
H 14	0	0	0	0	0	0	0	0	0	0	0	0	0	*1*	+3	0
O 15	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*2+4*	−3
H 16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	*1*

(6a) $= M_{\text{final}}$

	H 1	C 2	O 3	N 4	H 5	H 6	C 7	H 8	C 9	O 10	N 11	H 12	R 13	H 14	O 15	H 16
H 1	*1*															
C 2	1	*4*														
O 3		2	*2+4*													
N 4			*3+2*													
H 5			1	*1*												
H 6					*1*											
C 7			1		1	*4*										
H 8						1	*1*									
C 9							1		*4*							
O 10		1							1	*6*						
N 11									2		*3+2*					
H 12			1									*1*				
R 13											1		*1*			
H 14														*1*		
O 15														1	*2+4*	
H 16															1	*1*

(6b) $= M_{\sigma\text{-add.}}$

	H 1	C 2	O 3	N 4	H 5	H 6	C 7	H 8	C 9	O 10	N 11	H 12	R 13	H 14	O 15	H 16
H 1	*1*															
C 2	1	*4*														
O 3		2	*2+4*													
N 4			*3+2*													
H 5			1	*1*												
H 6					*1*											
C 7			1		1	*3*$^{\oplus}$										
H 8						1	*1*									
C 9								*3+2*$^{\ominus}$								
O 10		1							*1+6*$^{\ominus}$							
N 11								3		*4*$^{\oplus}$						
H 12			1								*1*					
R 13											1		*1*			
H 14														*1*		
O 15														1	*2+4*	
H 16															1	*1*

(6c) $= M_{\text{precursor}}$

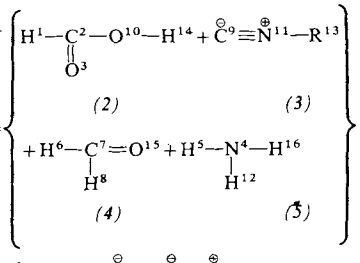
	H 1	C 2	O 3	N 4	H 5	H 6	C 7	H 8	C 9	O 10	N 11	H 12	R 13	H 14	O 15	H 16
H 1	*1*															
C 2	1	*4*														
O 3		2	*2+4*													
N 4			*3+2*													
H 5			1	*1*												
H 6					*1*											
C 7			1		1	*4*										
H 8						1	*1*									
C 9								*3+2*								
O 10		1							*2+4*							
N 11								3		*4*$^{\oplus}$						
H 12			1								*1*					
R 13											1		*1*			
H 14										1				*1*		
O 15							2								*2+4*	
H 16																*1*

(6d) $= M_{\text{initial}}$

In (6b)—(6d), the "zeros" of the *b*-region as well as the entries of the *i*-region that correspond to those of (6a) are omitted for simplicity. Additionally, if bond enthalpy data $\Delta H_{\mu\nu}$ had been included in the *i*-region, one would find that the sequence (6a)—(6d) corresponds to a favored, strongly exothermic pathway.

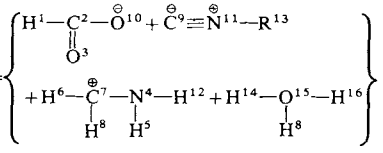
One of the transformations defined by the octet rule ($\Delta e_\lambda = 0$) which is preferred according to the entries of the *i*-region leads from (6a) to $M_{\alpha\text{-add}}$ (6b) and from here one obtains, *e.g.*, analogously $M_{\text{prec.}}$ (6c) and from this M_{initial} (6d). This sequence of transformations corresponds to the matter balance preserving synthetic pathway $EM_{initial} \rightarrow EM_{precursor} \rightarrow EM_{\alpha\text{-add}} \rightarrow EM_{final}$.

$EM_{initial}$ =

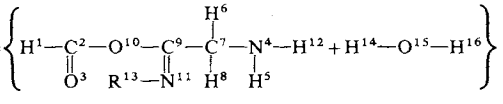


(2) (3) (4) (5)

$EM_{precursor}$ =



EM_{final} =

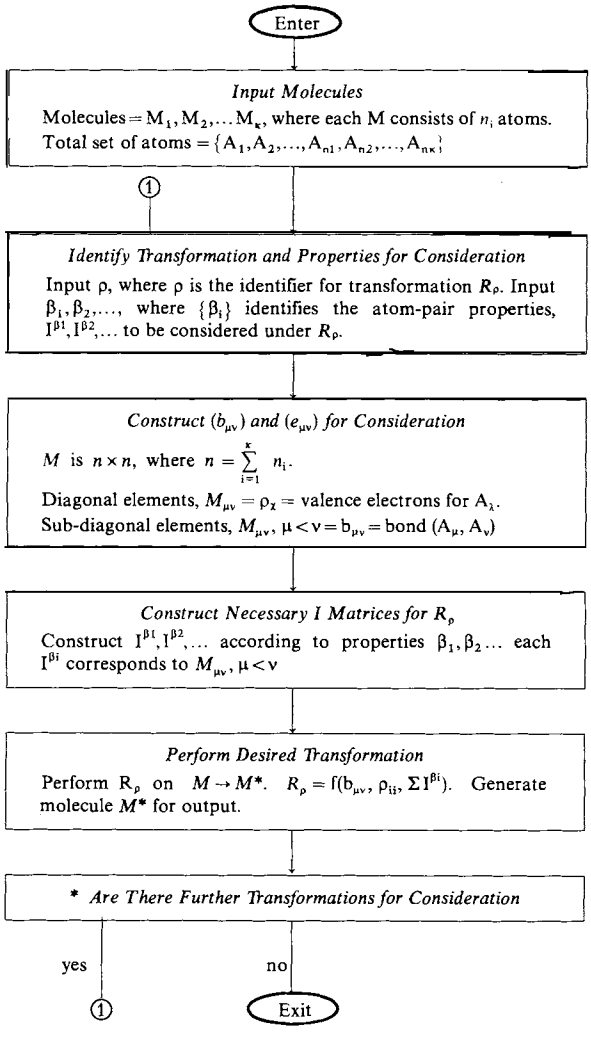


The above reaction is a four component condensation[18] of *(2)+(3)+(4)+(5)*. If this investigation had been carried out before 1959, then the four component condensation might have been proposed by a computer for experimental discovery.

For the prediction of conceivable mass spectrographic fragment patterns, the parent molecule or parent ion may be represented by its ***be*** matrix M_ρ. Those EM∈FIEM generated by suitably selected classes of dissecting transformation operators acting on M_ρ represent the fragments. This is in contrast to existing machine assisted mass spectral interpretation schemes that depend upon empirical data[19].

For the generation of a computer program, logical thought is transformed into algorithms. The latter are created from flow charts which represent the flow of logic and decision relative to a problem that will be solved by a computer.

An abbreviated flow chart for the program used to generate solutions to the ***be*** matrix transformations follows:



Note: If dissection is desired, transformations will be performed on successive M^*'s.

M_i molecule i
A_i atom *i*
n_i number of atoms in molecule i
ρ identifier for a transformation, *R*
R transformation identified by ρ.
β_i identifier for atom-pair property
μ, ν row, column numbers for matrix *M*.
M *be* matrix
M^* *be* matrix generated by some R_ρ on *M*.

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[1] Chemistry and Logical Structures, Part 4. This work was supported by the Department of Health, Education and Welfare, Biochemical Support Grant No RR-07012-04.—Part 3: see Ref. [2].

[2] *I. Ugi* and *P. Gillespie*, Angew. Chem. *83*, 980 (1971); Angew. Chem. internat. Edit. *10*, 914 (1971).

[3] *G. Kaufhold* and *I. Ugi* developed, in 1967 (unpublished results), an empirical computer method for generating and evaluating synthetic pathways for peptides using maximum yield as the criterion. (a) *I. Ugi*, Rec. Chem. Progr. *30*, 289 (1969); (b) *G. Gokel, P. Hoffmann, H. Klieman, H. Klusacek, G. Ludke, D. Marquarding*, and *I. Ugi* in *I. Ugi*: Isonitrile Chemistry. Academic Press, New York, 1971, pp 211; (c) *I. Ugi*, Chem. Rep. Intra-Science Foundation *1971*, Vol. 4 (in press).

[4] *R. E. Ireland*: Organic Synthesis. Prentice-Hall, Englewood Cliffs, N. Y., 1969, p. 17.

[5] *E. J. Corey* and *W. T. Wipke*, Science *166*, 178 (1969).

[6] In this context we wish to mention the treatment of matter balance problems with a matrix method by *G. Kaufhold* and *I. Ugi*, Liebigs Ann. Chem. *709*, 11 (1967).

[7] *D. Evans* has recently pointed out in lectures and discussions, *e.g.*, at the UCLA Physical Organic Chemistry Seminar on May 6, 1971, that the precursors of a given target molecule can be derived on the basis of Lapworth's "charge affinity" assignments [8]. Ref. [3b] contains a discussion of the possibilities of application of Evans' conception in the planning of syntheses with the aid of EDV on the basis of the universal equation (2).

[8] *A. Lapworth*, J. Chem. Soc. *121*, 416 (1922).

[9] The Dewar-Evans rules [10], as recently formulated by Dewar [11, 12], and based on Evans' rule of isoconjugation [13] together with the PMO treatment of aromaticity and the concept of anti-Hückel systems, correspond to a simple and comprehensive theory of concerted reactions. These can be regarded either as providing a

satisfactory basis for the Woodward-Hoffmann rules [14] or a satisfactory alternative to them and related [15, 16] or corresponding treatments [16, 17] of the underlying problem.

[10] See also: *I. Ugi, D. Marquarding, H. Klusacek, G. Gokel,* and *P. Gillespie,* Angew. Chem. *82,* 741 (1970); Angew. Chem. Internat. Edit. *9,* 703 (1970).

[11] *M. J. S. Dewar,* Angew. Chem. *83,* 859 (1971); Angew. Chem. internat. Edit. *10,* 845 (1971).

[12] *M. J. S. Dewar,* Tetrahedron Suppl. *8,* 75 (1966).

[13] *M. G. Evans* and *M. Polanyi,* Trans. Faraday Soc. *34,* 11 (1938); *M. G. Evans* and *E. Warhurst, ibid. 34,* 614 (1938); *M. G. Evans, ibid. 35,* 824 (1939).

[14] *R. B. Woodward* and *R. Hoffmann,* Angew. Chem. *81,* 797 (1969); Angew. Chem. internat. Edit. *8,* 781 (1969).

[15] *H. C. Longuett-Higgins* and *E. W. Abrahamson,* J. Amer. Chem. Soc. *87,* 2045 (1965).

[16] *K. Fukui* in *P.-O. Löwdin* and *B. Pullman:* Molecular Orbitals in Chemistry, Physics, and Biology Academic Press, New York 1964, p. 513; Accounts Chem. Res. *4,* 57 (1971).

[17] *J. J. C. Mulder* and *I. Oosterhoff,* Chem. Commun. *1970,* 305, 307.

[18] Cf. *e.g.: I. Ugi,* Angew. Chem. 74, 9 (1962); Angew. Chem. internat. Edit. *1,* 8 (1962).

[19] *A. Buchs, A. M. Duffield, G. Schroll, C. Djerassi, A. B. Delfine, B. G. Buchanan, G. L. Sutherland, E. Q. Fergenbaum,* and *J. Lederberg,* J. Amer. Chem. Soc. *92,* 6831 (1970).

Oxidation of $C_5H_5Mn(CO)_2N_2H_4$ to $C_5H_5Mn(CO)_2N_2$, a New Dinitrogen Complex[1]

By *Dieter Sellmann*[*]

In order to study the redox behavior of complexed hydrazine, $C_5H_5Mn(CO)_2N_2H_4$ *(1)*[2] was subjected to the action of various oxidizing agents. The two-electron oxidant H_2O_2/Cu^{2+} was found to convert *(1)* into π-cyclopentadienyldicarbonyldinitrogenmanganese(I) *(2)* in 40% yield according to:

$$C_5H_5Mn(CO)_2N_2H_4 + 2\,H_2O_2 \xrightarrow[THF/-40\,^\circ C]{Cu^{2+}/1\,h} \underset{(2)}{C_5H_5Mn(CO)_2N_2} + 4\,H_2O$$

(1)

After removal of the solvent tetrahydrofuran, *(2)* sublimed at room temperature ($\approx 10^{-3}$ torr) to give large, reddish-brown crystals that are diamagnetic and highly refractive. They are also air-stable, resublimable, melt at 60°C with evolution of gas, and dissolve in all common organic solvents. Their composition and structure were confirmed by elemental analysis, IR, ^{1}H-NMR, and mass spectroscopy[3].

The IR spectrum of the complex *(2)* in *n*-hexane shows three characteristic very strong bands of approximately equal intensity at 2169 ($\nu_{N\equiv N}$), 1980 ($\nu_{C\equiv O}$, A_1), and 1923 cm^{-1} ($\nu_{C\equiv O}$, B_1); in KBr these bands are shifted to 2163, 1965, and 1895 cm^{-1}.

The method of preparation and the extremely intense $\nu_{N\equiv N}$ band suggest "end-on" bonding of the N_2 ligand to the central metal atom.

In the ^{1}H-NMR spectrum ([D_6]-acetone) the C_5H_5 protons of *(2)* show a sharp singlet at $\tau = 5.16$, which is shifted upfield by 12 Hz compared to the signal of $C_5H_5Mn(CO)_3$ *(3)*.

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In the mass spectrum (50 eV) the molecular ion occurs at *m/e* 204. The ionization-induced degradation of *(2)* resembles that of *(3)*; however, the intensity ratios of the ions at *m/e* 204, 176, and 148 exhibit characteristic differences for the two compounds.

Contrary to the prevailing opinion[4], the spectroscopic data show that the N_2 can act quite well as a stronger donor than CO if attention is paid to the sum of the σ-donor and π-acceptor strengths. The weakening of the $\nu_{C\equiv O}$ frequencies compared to *(3)*, as well as the drop in force constants k and k_i calculated according to ref. [5], which are respectively 15.61 and 0.49 mdyn/Å for *(3)* and 15.38 and 0.45 mdyn/Å for *(2)*, and the upfield shift of the C_5H_5 protons, evidence an increase in electron density on the central metal atom due to the N_2 ligand.

(2) is the first N_2-complex to have been synthesized by controlled oxidation of the corresponding hydrazine derivative. Further studies on related complexes will show whether the technique is applicable to the systematic synthesis of N_2 complexes. Preliminary experiments on *(2)* indicate a high reactivity in solution and ready substitution of the N_2 ligand by other donors.

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Fluorochlorobromoiodosilane[**]

By *Friedrich Höfler* and *Walter Veigl*[*]

Halosilanes of the type SiX_3Y and SiX_2Y_2 have been known for a long time[1], but only a few investigations regarding SiX_2YZ compounds have been published in the literature[2-4]. In our investigations of halogen exchange reactions at the silicon atom[5] we have now succeeded in synthesizing the hitherto unknown fluorochlorobromoiodosilane SiFClBrI *(1)*:

$$SiBr_4 \xrightarrow{SbF_3} \underset{(2)}{SiFBr_3} + SiF\,Br_{4-n}\,(n=2\text{–}4) \qquad (1)$$

$$\underset{(2)}{SiFBr_3} \xrightarrow{SbCl_3} \underset{(3)}{SiFClBr_2} + SiFCl_nBr_{3-n}\,(n=2,3) \qquad (2)$$

$$\underset{(3)}{SiFClBr_2} + HSiI_3 \longrightarrow \underset{(1)}{SiFClBrI} + HSiBrI_2 \qquad (3)$$

By modifying the reaction conditions (slow addition of Sb-halide to boiling halosilane, rapid removal of reaction products) used by *Schumb* and *Anderson*[2,6] in reactions (1) and (2) we have been able to obtain better yields of *(2)*

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and *(3)*. On heating *(3)* with SbI_3 at 100°C for 24 hours in a sealed tube no iodination took place, whereas 12 hours' heating of *(3)* with SiI_4 at 100°C gave *(1)* in 5% yield. In each case, however, the main reaction was disproportionation of *(3)* to *(2)* and $SiFCl_2Br$ *(4)*. On the other hand, reaction of *(3)* and $HSiI_3$ at 100°C for 18 hours resulted in 50% conversion according to Eq. (3); small amounts of other products formed by progressive Br/I exchange that could be detected spectroscopically were (in order of decreasing amounts): $HSiBr_2I$ and $HSiBr_3$ (by ^{1}H-NMR), $SiFClI_2$ *(5)*, $SiFBr_2I$, $SiFBrI_2$, *(2)*, *(4)*, and $SiFI_3$ (^{19}F-NMR). *(1)* can be separated from the reaction mixture in very pure form by fractional distillation, since, with exception of *(3)* (b.p. 59.5°C), all the main components of the mixture boil at higher temperatures.

(1) is a colorless, readily hydrolyzable liquid ($b.p._{.735}$ = 85°C, $n_D^{20} = 1.507$) which turns pink in color when exposed to air or light. Its thermal stability is remarkable: the substance remains unchanged after 8 hours' heating at 100°C in an ampoule. After 33—50 hours at this temperature, 5—8% *(3)* and *(5)* could be detected in the Raman spectrum by means of their most intense lines at 361 and 316 cm^{-1}, respectively.

All fundamental vibrations of *(1)* are Raman and IR active. As expected, the Raman spectrum shows nine polarized lines (Table 1); the IR absorptions of the four stretching vibrations were also measured. The quoted assignments are derived from a vibration analysis, which, in combination with force constants and averaging methods described in Ref. [7], lead to good agreement of calculated and measured frequencies (stretching force constants: f(SiF) = 5.7, f(SiCl) = 3.0, f(SiBr) = 2.42, f(SiI) = 1.76 mdyn/Å). In addition to the relatively strong mixing of bending coordinates, the coupling of the lowest stretching vibration (νSiI) with the highest bending mode (δFSiCl) is noteworthy.

Table 1. Fundamental vibrations of SiFClBrI in the IR (1000—250 cm^{-1}) and Raman spectra.

	IR (cm^{-1})	Raman (cm^{-1})	Int.	Depol. factor	Calc. (cm^{-1})	Assignment
ν_1	910 s	912	0.03	—	916	νSiF
ν_2	587 s	588	0.11	—	578	νSiCl
ν_3	486 s	482	0.08	—	481	νSiBr
ν_4	333 m	334	10	0.05	337	νSiI, δFSiCl
ν_5		236	2.8	0.32	245	δFSiBr, δFSiCl
ν_6		208	3.6	0.42	214	δFSiI
ν_7		179	5.7	0.26	184	δClSiBr, δFSiCl
ν_8		129	3.9	0.70	131	δClSiI, δClSiBr
ν_9		99	7.8	0.63	100	δBrSiI, δClSiI

The ^{19}F-NMR spectra of *(1)*—*(5)* consist of singlets with ^{29}Si satellites; with increasing electronegative substitution, the signals are shifted to higher field and the coupling constants $J(^{29}Si^{19}F)$ decrease (Table 2).

Table 2. Chemical shifts δ (against CCl_3F) and coupling constants $J(^{29}Si^{19}F)$ from the ^{19}F-NMR spectra of fluorohalosilanes *(1)*—*(5)*.

	(1)	*(2)* [8]	*(3)*	*(4)*	*(5)*
δ (ppm)	74.5	76.5	81.5	87.0	70.0
J (Hz)	380	365	351	332	401

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Effect of Non-Planarity on the Paramagnetic Ring Current in the Dianion of 1,6;8,13-Propanediylidene[14]annulene[**]

By *Fabian Gerson, Klaus Müllen*, and *Emanuel Vogel*[*]

A concept of "ring current" induced in cyclic π-electron systems[1] (perimeters) is usually invoked to account for the ^{1}H-NMR chemical shifts of ring protons in these systems[2]. Theory predicts a "diamagnetic" or "paramagnetic" ring current according to whether the perimeter has $4n+2$ or $4n$ π-electrons[3]. In a perimeter with $4n+2$ electrons, the signals of the outer and inner ring protons undergo a down-field and an up-field shift, respectively, relative to the signals of olefinic protons. The reverse is true for a perimeter with $4n$ electrons[2]. Bond alternation and deviations of the perimeter from planarity should reduce the paramagnetic ring current much more effectively than the diamagnetic one[3]. This statement has been verified by us for 1,6;8,13-propanediylidene[14]annulene *(1)*[4], a bridged fourteen-membered perimeter with $4\times3+2=14$ π-electrons, and for its dianion $(1)^{2\ominus}$ having $4\times4=16$ π-electrons. As shown by molecular models, X-ray structure[5], and other spectroscopic studies[6], the perimeter in *(1)* exhibits moderate deviations from planarity. The same geometry can be assumed for $(1)^{2\ominus}$, since the shape of the perimeter is fixed by the bridging groups.

The dianion $(1)^{2\ominus}$ has been produced by reduction of *(1)* with potassium in perdeuteriotetrahydrofuran ([D_8]-THF) or 1,2-dimethoxyethane (DME). This method has also been used for the preparation of the anthracene dianion $(2)^{2\ominus}$ from the parent neutral hydrocarbon *(2)*. The relevant proton resonance data for *(1)*, $(1)^{2\ominus}$, *(2)*, $(2)^{2\ominus}$ are listed in Table 1, along with the corresponding values for *trans*-10b,10c-dimethyl-10b,10c-dihydropyrene *(3)*[7] and its dianion $(3)^{2\ominus}$[8].

In the following brief discussion, the data for *(1)* and $(1)^{2\ominus}$ will be compared with those for *(3)* and $(3)^{2\ominus}$. Unlike *(1)* and $(1)^{2\ominus}$, the rigid fourteen-membered perimeter in both *(3)*[10] and $(3)^{2\ominus}$[8] achieves a high degree of planarity.

Comparison of the τ-values for the ring protons in the neutral compounds *(1)* and *(3)* indicates that moderate deviations of the perimeter from planarity affect the diamagnetic ring current to a small extent only. (The difference of 0.7 ppm is partially due to unequal perimeter areas in the two compounds[11].) In contrast, as shown by an analogous comparison for the ring protons in the dianions $(1)^{2\ominus}$ and $(3)^{2\ominus}$, even moderate deviations from a

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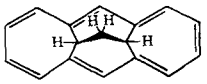
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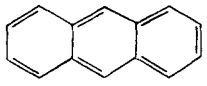
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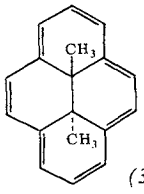
coplanar arrangement have a striking effect on the paramagnetic ring current. It should be borne in mind that—on going from the neutral compounds to their dianions—an average shift of approximately $2 \times 10/14 \approx 1.4$ ppm per ring proton is expected by a mere allowance for two additional negative charges[2]; such a shift (+1.6 ppm) indeed occurs



(1)



(2)



(3)

Table 1. Centers of gravity for proton resonances of *(1)*, $(1)^{2\ominus}$, *(2)*, $(2)^{2\ominus}$, *(3)* and $(3)^{2\ominus}$. τ-values in ppm. The uncertainty in the number given for the bridge protons of $(1)^{2\ominus}$ is due to a partial masking of the pertinent signals by the resonances of the solvents (isotopic impurities in $[D_8]$-THF, wing of the CH_3 band in DME).

Species	Ring protons	Shift	Bridge protons	Shift	Solvent/ temp. (°C)	Ref.
(1)	2.4	+ 2.1	10.9	− 3.1	$CDCl_3$/+25	[4]
$(1)^{2\ominus}$	4.5		7.8 (± 0.3)	(± 0.3)	$[D_8]$-THF/−60	this work
(2)	2.2	+ 1.6	—		CS_2/+25	[9]
$(2)^{2\ominus}$	3.8		—		DME/−60	this work
(3)	1.5	+12.1	14.3	−25.3	$CDCl_3$/+25	[7, 8]
$(3)^{2\ominus}$	13.6		−11.0		$[D_8]$-THF/−65	[8]

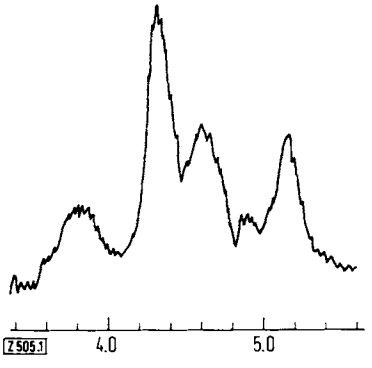


Fig. 1. Proton resonance spectrum of the dianion $(1)^{2\ominus}$ in the τ-range of 3.5−5.5 ppm; recorded for a $[D_8]$-THF solution at −60 °C and a frequency of 60 MHz.

for the conversion of anthracene *(2)* to its dianion $(2)^{2\ominus}$. The fact that the corresponding shift (+2.1 ppm) for the conversion of *(1)* to $(1)^{2\ominus}$ is only 0.5 ppm larger points to an almost complete quenching of the paramagnetic ring current in $(1)^{2\ominus}$. On the other hand, an analogous shift of more than +10 ppm is observed in the case of *(3)* and $(3)^{2\ominus}$ (Table 1).

Similar conclusions can be drawn from the shift of the bridge protons, although their different positions in the two bridged annulenes make a direct comparison more problematical than for the ring protons.

It is noteworthy that the resonance signals of the ring protons in $(1)^{2\ominus}$ extend over a range of 1.5 ppm (Figure 1), whereas the corresponding range for the neutral compound *(1)* is only 0.5 ppm[4]. This increase for $(1)^{2\ominus}$ points to larger differences in the chemical shifts. Unfortunately, an analysis of the spectrum of $(1)^{2\ominus}$ is impeded by line-broadening due to the presence of the intermediate radical anion $(1)^{\ominus}$[6].

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Crystal and Molecular Structure of Bis(π-cyclopentadienyl)tetrasulfidotungsten(IV)[**]

By *Betty R. Davis, Ivan Bernal,* and *Hartmut Köpf*[*]

In 1969, *Köpf*[1] prepared the first metallocene tetrachalcogenide chelate $(\pi\text{-}C_5H_5)_2MoS_4$ and proposed from NMR studies that the cyclic MoS_4 moiety was nonplanar but nevertheless symmetrically disposed with respect to the two cyclopentadienyl rings. This conclusion was based on the evidence that the solution ^{1}H-NMR spectrum of the compound consists of a single, sharp line which showed no broadening down to −95 °C. Later, similar results were found for $(\pi\text{-}C_5H_5)_2WS_4$ *(1)*[2]. In continuation of our

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studies of polychalcogenides[3,4], the structure of the tungsten compound *(1)* was determined. Of additional interest was the question of the S—S bond lengths in the S_4 fragment since an alternation of bond lengths in a tetrasulfide bridge of an aromatic system analogous to paracyclophane has been previously reported[5].

Diamond-shaped, orange plates of the compound were found to crystallize in the monoclinic system, space group $P2_1/n$, with $a=11.242$ (3), $b=12.154$ (5), $c=8.790$ (2), and $\beta=92.93$ (3)°; $V=1199.34$ Å^3; $d_{exp}=2.46$ g cm^{-3} and d_{calc} ($Z=4$) $=2.44$ g cm^{-3}. Each reflection was collected twice to give a total of 5700 data ($d^*_{max}=1.20$). These data were averaged and corrected for absorption ($\mu=108.1$ cm^{-1}) to give an independent data set of 2288 reflections of which 989 were used in the present analysis. The structure was solved using conventional heavy atom techniques. To date, the tungsten and four sulfur atoms have been refined with anisotropic thermal parameters, the carbon atoms have been refined with isotropic thermal parameters, and the hydrogen atoms have been held to their idealized positions and assigned an isotropic thermal parameter of 5.0 Å^2. This refinement gives residuals of $R_1=0.049$ and $R_2=0.048$, and the error in an observation of unit weight is 1.12 electrons. A difference Fourier synthesis at this stage shows peaks as high as 2.9 electrons/Å^3 associated with ripples from the tungsten atom.

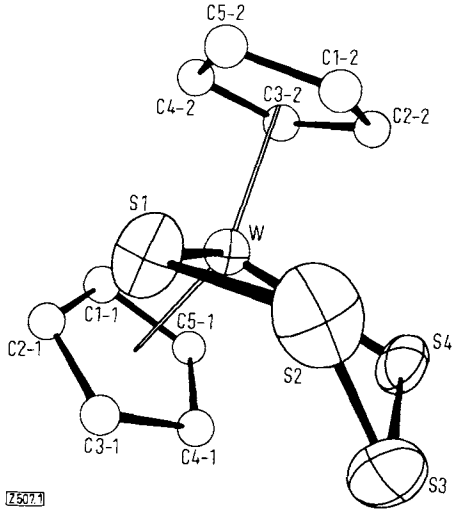


Fig. Molecular configuration of $(\pi\text{-}C_5H_5)_2WS_4$ *(1)*. The thermal ellipsoids shown for the W and four S atoms are 50% probability envelopes. The isotropic thermal parameters used for the C atoms are of an arbitrary size chosen because of representational convenience.

The molecule is shown in the Figure where it is obvious that previous conformational predictions[1,2] are verified and thus the NMR results obtained for *(1)* and related compounds are readily understood. A selection of bond lengths and angles for *(1)* are given in the Table.

A comparison of *(1)* with compounds of the type $(\pi\text{-}C_5H_5)_2W(SC_6H_5)_2M(CO)_4$ *(2)* (M = W, Mo, Cr) studied by *Cameron et al.*[6] is of interest since the latter also possess a $(\pi\text{-}C_5H_5)_2WS_2$ bonding system. The S—W—S angle in all three compounds *(2)* has an average value of 72.5° while in *(1)* this angle has opened to give a value of 89.1 (2)°. This opening is apparently responsible for the shorter W—S bond distance of 2.413 (6) Å found in *(1)*; the average W—S bond distance in the three compounds of type *(2)* is 2.49 Å. The Cp—W—Cp angle (Cp = cyclopentadienyl ring centroid) is essentially preserved since in *(2)* it is approximately 133° and in *(1)* it is 135°. Likewise, the average W—Cp distance remains almost constant [2.03 Å in *(1)* and about 2.00 Å in *(2)*]. It is interesting to note that the Cp—M—Cp angle is relatively constant for species of the type $(\pi\text{-}C_5H_5)_2MX_2$ since for $(\pi\text{-}C_5H_5)_2TiS_5$ the value is[3,4] 133.7° and for $(CH_2)_3(\pi\text{-}C_5H_4)_2TiCl_2$[7] it is 132.64°.

Distances (Å)			
W–S1	2.413(6)	S1–S2	2.105(7)
W–S4	2.413(5)	S2–S3	2.016(8)
W–Cp1 [a]	2.025	S3–S4	2.116(9)
W–Cp2 [a]	2.035		
Angles (°)			
S1–W–S4	89.1(2)	S1–S2–S3	100.3(3)
Cp1–W–Cp2	135.1	S2–S3–S4	100.1(3)
W–S1–S2	109.6(3)		
W–S4–S3	108.7(3)		

[a] Ring centroid.

There is a small but distinct variation in the three S—S bond lengths. The two outer bonds have an average value of 2.109 (9) Å which is longer than the central bond of 2.016 (8) Å; this is a reversal in the mode of the bond length alternation reported for an aromatic tetrasulfide[5]. The variation in bond lengths in the S_4 system of *(1)*, which is also observed in $(\pi\text{-}C_5H_5)_2MoS_4$[8], could be due to a perturbation of the normal S—S π interactions by $(d\rightarrow d)_\pi$ back bonding from the d^2 central atom to the adjacent sulfur atoms. This would also account for the shortening of the W—S bond length compared to compound *(2)* in which the M→S back bonding probably originates from the d^6 zerovalent carbonylmetal.

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Ethoxydimethylaminocarbenepentacarbonylchromium(0)[1]

By *Ernst Otto Fischer, Eberhard Winkler, Cornelius G. Kreiter, Gottfried Huttner*, and *Bernhard Krieg*[*]

We recently reported the synthesis of the first carbonylmetal derivative of an acyclic carbene stabilized by two hetero atoms, $(CO)_5Cr—C(OC_2H_5)N(C_2H_5)_2$, and deduced the nature of the bonding in this compound from ^{1}H-NMR, IR, and MS studies[1].

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Since the X-ray structure analysis of this compound proved difficult because of the low melting point (29 °C), we prepared the yellow, diamagnetic compound ethoxydimethylaminocarbenepentacarbonylchromium(0), which melts at 45 °C, and elucidated its structure by spectroscopic means and also by X-ray analysis.

$$Cr(CO)_6 + LiN(CH_3)_2 \xrightarrow[0\,^\circ C]{THF} (CO)_5Cr{=}C\begin{matrix}\diagup OLi \cdot x\,THF \\ \diagdown N(CH_3)_2\end{matrix}$$

$$\xrightarrow[\substack{CH_2Cl_2\\0\,^\circ C}]{+\,[(C_2H_5)_3O]\,BF_4} (CO)_5Cr{=}C\begin{matrix}\diagup OC_2H_5 \\ \diagdown N(CH_3)_2\end{matrix} + LiBF_4 + O(C_2H_5)_2$$

The complex has a dipole moment of 5.87 ± 0.1 D at 20 °C in cyclohexane, sublimes at 30 °C, and starts to decompose at about 110 °C. Its IR spectrum (*n*-hexane; LiF optics) shows two ν_{CO} frequencies (cm^{-1}) at 2057 m (A_1) and 1928 vs (A_1, E). In view of the thus indicated minimal distortion of the $(CO)_5Cr$ system, we determined the CO force constants for the presumed C_{4v} symmetry[2]: $k_1 = 15.22$, $k_2 = 15.63$, $k_i = 0.31$ mdyn/Å; k_1 is the force constant for the CO group *trans* to the carbene and k_2 that for the *cis* one; k_i is the interaction constant of the CO groups.

In C_6D_6 [$CDCl_3$] the ^{1}H-NMR spectrum (τ values) exhibits a quartet at 5.68 (2) [5.38 (2)] for the OCH_2 protons, a triplet at 9.07 (3) [8.58 (3)] for OCH_2CH_3, a singlet at 7.85 (3) [6.94 (3)] for NCH_3 *(cis)*, and another singlet at 7.12 (3) [6.43 (3)] for NCH_3 *(trans)*.

In molten naphthalene, initial reversible broadening of the NCH_3 signals is followed on further heating by coalescence (only one NCH_3 signal) at +141 °C. This leads to an activation energy of $\Delta G^{\neq} = 20.8$ kcal/mol[3] for rotation about the $C_{carbene}$—N bond, thereby demonstrating a large π-bonding contribution to this bond. On cooling of the complex in [D_8]-toluene/carbon disulfide mixtures we were able to observe line broadening of the OC_2H_5 signals below about −80 °C but no signal splitting was to be seen, even at about −120 °C. Nevertheless, these data would suggest that the activation energy for rotation about the $C_{carbene}$—O bond must be lower than 8 kcal/mol; this bond therefore also has π character, although much less than the $C_{carbene}$—N bond.

Since a *cis*-OC_2H_5 group would involve increased steric hindrance with the *cis*-NCH_3 protons and since the small shift of the OCH_2 signals induced by [D_8]-toluene also suggests a *trans* conformation, this configuration should at least predominate in solution.

The results of a three-dimensional X-ray structure analysis ($R_1 = 0.054$; 2329 independent non-zero structure factors; space group $P\bar{1}$; $Z = 2$) show that only the sterically more favorable *trans* configuration is present in the crystal (Fig. 1).

The carbene ligand is essentially planar, its plane passing approximately through the bisector of the angle between two mutually *cis* CO groups. Despite the presence of two electron-donating substituents on the carbene carbon, the $C_{carbene}$—Cr distance (2.133 ± 0.004 Å) is not longer than those found for pentacarbonylchromium(0) complexes of monoamino-substituted carbenes (2.15 ± 0.01 Å in pentacarbonyl[cyclohexylamino-(1-methoxyvinyl)carbene]chromium(0)[4] and 2.16 ± 0.01 Å in pentacarbonyl[diethylaminomethylcarbene]chromium(0)[5]). The $C_{carbene}$-hetero atom distances are considerably shorter

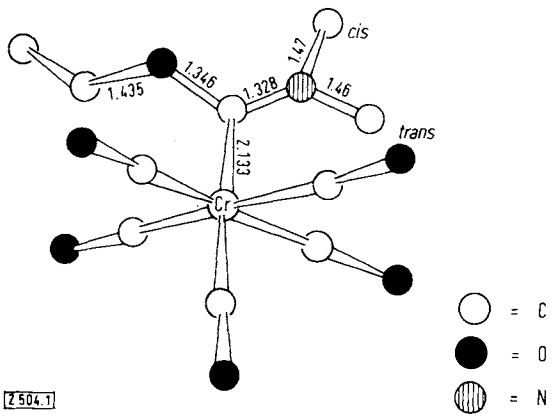


Fig. 1. Molecular structure of ethoxydimethylaminocarbenepentacarbonylchromium(0).

than the corresponding single bonds (see Fig. 1); the π-bond component of the $C_{carbene}$—N bond is significantly greater than that of the $C_{carbene}$—O bond. The carbene ligand exerts a geometrical *trans* effect: The axial Cr—C_{CO} bond (1.847 ± 0.005 Å) is significantly shorter than any of the equatorial Cr—C_{CO} bonds, for which values of 1.873 ± 0.005 to 1.897 ± 0.005 Å were found with a mean value of 1.887 ± 0.01 Å.

The mass spectrum[6] (Atlas CH4, ion source TO4, 50 eV, direct sample injection) exhibits the molecular ion (*m/e* 293) and fragments corresponding to successive loss of CO ligands $[(CO)_nCr{-}C(OC_2H_5)N(CH_3)_2]^+$ ($n = 4-0$) at *m/e* 265, 237, 209, 181, and 153. The fragment $[Cr{-}C(OC_2H_5)N(CH_3)_2]^+$ responsible for the base peak of the spectrum decomposes in a manner characteristic of metal-carbene ions, either by complete loss or by partial fragmentation of the intact carbene ligand.

Procedure

All operations must be carried out with exclusion of air in N_2-saturated solvents previously dried over $CaH_2/LiAlH_4$. A solution of $LiN(CH_3)_2$ (1.02 g, 20 mmol) in THF (100 ml) is added dropwise at 0 °C to a stirred suspension of $Cr(CO)_6$ (4.40 g, 20 mmol) in THF (100 ml). If the 1:1 adduct is to be isolated, the reddish brown solution is concentrated to a volume of about 50 ml (oil-pump vacuum) at 0 °C and the product precipitated with *n*-pentane; repeated recrystallization from ether at −50 °C gives $(CO)_5CrC(N(CH_3)_2)$-$OLi \cdot 2O(C_2H_5)_2$ as colorless needles.

To prepare the carbene complex the reaction solution is completely freed from solvent under oil-pump vacuum at 0 °C, and the residual oily adduct dissolved directly without further purification in methylene chloride (25 ml) and added dropwise, with stirring, to a solution of $[(C_2H_5)_3O]BF_4$ (3.80 g, 20 mmol) in methylene chloride (20 ml). After 10 minutes' stirring, the solvent is evaporated under vacuum and the brown, oily residue is extracted with two 20-ml portions of *n*-hexane. The combined extracts are filtered through a G 3 frit, concentrated to a volume of

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[5] *J. A. Connor* and *O. S. Mills*, J. Chem. Soc. *A 1969*, 334.

[6] Experiments by Dr. *J. Müller*, München.

10 ml, and chromatographed on a silica gel column (Merck 0.05 to 0.2 mm; column dimensions 40 × 2 cm) at 0 °C with hexane/benzene (4:1). The yellow zone is collected, the solvent removed in a high vacuum, and the residue recrystallized twice from *n*-pentane: pale yellow needles, m.p. 45 °C; yield 250 mg (4%).

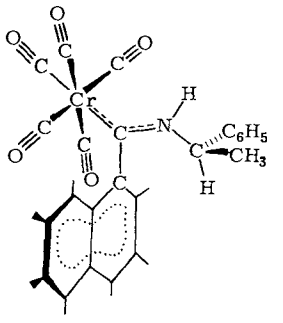
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Atropisomerism of Transition Metal Carbene Complexes[1]

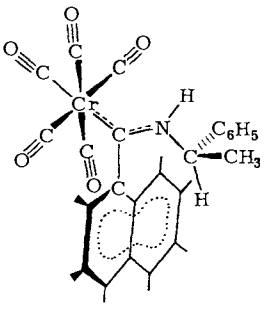
By *Henri Brunner*, *Ernst Otto Fischer*, and *Manfred Lappus*[*]

o-Substituted derivatives of biphenyl and similar compounds exist in atropisomeric forms[2]. Appropriately substituted carbene complexes of transitions metals were also expected to exhibit atropisomerism.

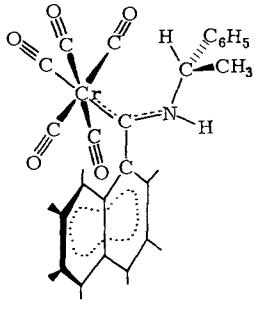
Reaction of (methoxy-1-naphthylcarbene)pentacarbonylchromium(0)[3] with (+)-α-phenylethylamine in diethyl ether yields [(α-phenylethylamino)-1-naphthylcarbene]-pentacarbonylchromium(0). Of the two possible *cis-trans* isomers (with regard to the C—N bond) *(1)* and *(2)*, the *cis* isomer *(1)* is formed preferentially. The barrier to free rotation between the carbene carbon and the 1-naphthyl group gives rise to a further kind of isomerism: For the



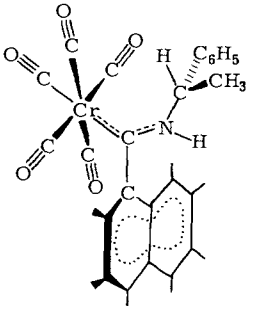
(1a)



(1b)



(2a)



(2b)

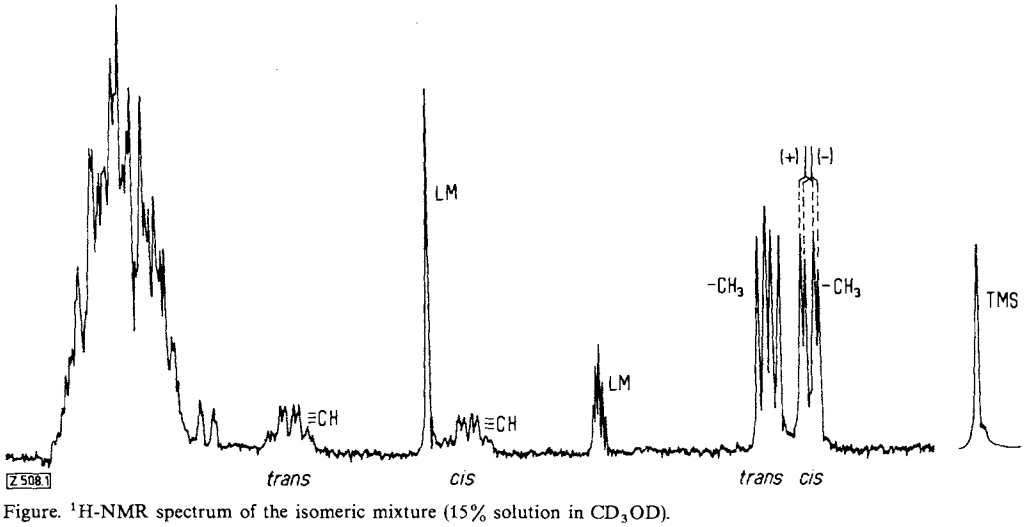


Figure. ^{1}H-NMR spectrum of the isomeric mixture (15% solution in CD_3OD).

cis and *trans* products *(1)* and *(2)* there are two atropisomers each, *viz. (1a)*, *(1b)* and *(2a)*, *(2b)*, which differ in the spatial arrangements of the 1-naphthyl group.

Nuclear magnetic resonance is particularly suitable for identification of the isomers. The ^{1}H-NMR spectrum of a 1:1 mixture of the *cis-trans* isomers *(1)* and *(2)* in CD_3OD (Fig.) exhibits four doublets for the diastereoisomers *(1a)*, *(1b)*, *(2a)*, and *(2b)* in the methyl region; the signals are grouped as two pairs each with similar chemical shifts for the *cis* and *trans* compounds. The differences between the chemical shifts of the methine protons in the *cis-trans* isomers are greater than those for the methyl protons. The low intensity and poor resolution of the methine signals, however, precludes their use in quantitative studies or for distinguishing between the atropisomers. Separation of the *cis-trans* isomers or the atropisomers on the basis of differing solubilities, however, can readily be followed with the aid of the methyl signals.

The *cis* and *trans* forms can be recognized from the change in chemical shift of the N—CH—CH_3 group on transition from acetone to chloroform solvent[4]: The signals of the *cis*-N—CH—CH_3 group display a larger upfield shift than the *trans*-N—CH—CH_3 group when the solvent is changed.

It may thus be seen from the Table that the signal systems of the methyl and methine protons at higher field are to be assigned to the *cis* compounds *(1a)* and *(1b)*, and those at lower field to the *trans* isomers *(2a)* and *(2b)*.

The *cis-trans* isomers are formed in the ratio of about 6:1 on preparation of [(α-phenylethylamino)-1-naphthylcarbene]pentacarbonylchromium(0) at room temperature.

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Recrystallization of the *cis-trans* mixture from diethyl ether/pentane after chromatography on SiO_2 affords a pure sample of the more sparingly soluble *cis* compound *(1)*; in contrast, the more readily soluble *trans* isomer *(2)* has not yet been separated completely from the *cis* isomer. We therefore limited our attempts to resolve the atropisomers to the *cis* compounds *(1)*. After repeated fractional crystallization (18 ×) from diethyl ether/pentane the more sparingly soluble fraction containing the levorotatory diastereoisomer exhibited a specific rotation of $[\alpha]_{546}^{20} = -168°$. The highest rotations recorded so far for the fractions of the mother liquor enriched in the more readily soluble dextrorotatory diastereoisomers are $[\alpha]_{546}^{20} = +46°$. The rotations were measured with approximately 10^{-3} M solutions in benzene. The four doublets of the methyl groups of *(1a)*, *(1b)*, *(2a)*, and *(2b)* are retained in the ^{1}H-NMR spectrum at 70 °C in CD_3OD solution. Like the thermal interconversion of *cis* and *trans* isomeric amino carbene complexes[5], the transition between the atropisomers *(1a)*—*(1b)* and *(2a)*—*(2b)* is so slow that it cannot be determined from the temperature dependence of the ^{1}H-NMR spectrum.

Table. τ values from the ^{1}H-NMR spectrum of the isomeric mixtures in various solvents (15% solutions).

		CD_3COCD_3	$CDCl_3$	Δτ
N—CH—CH_3	*(1)*	8.38	8.66	0.28
	(2)	8.05	8.28	0.23
N—CH—CH_3	*(1)*	5.55	5.72	0.17
	(2)	4.08	4.20	0.12

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[1] Optically active transition metal complexes, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. — Part 6: *H. Brunner* and *H.-D. Schindler*, J. Organometal. Chem. *24*, C 7 (1970). Also Part 37 of the series: Transition metal carbene complexes. — Part 36: *E. O. Fischer*, *M. Leupold*, *C. G. Kreiter*, and *J. Müller*, Chem. Ber., in press.

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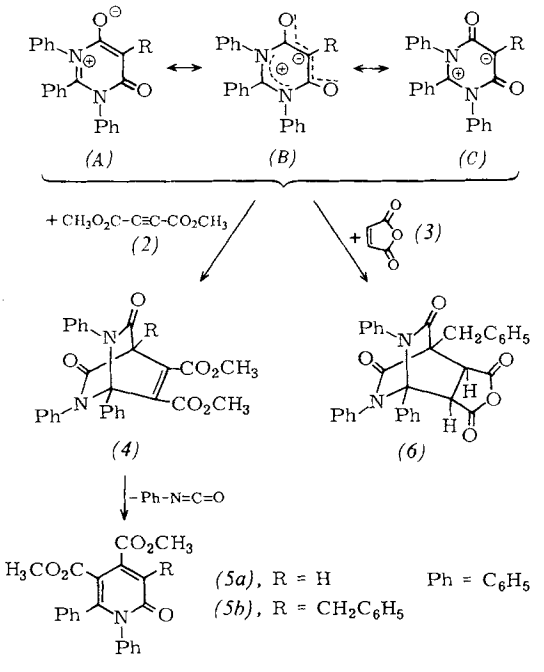
Cycloadditions with Mesomeric Pyrimidine Betaines[1]

By *Thomas Kappe* and *Wolfgang Lube*[*]

Recently, we reported on the synthesis of mesomeric pyrimidine betaines *(A)*, whose structure can only be described by a series of zwitterionic canonical formulas[2]. The distribution of charge in these compounds is best expressed in terms of formulation *(B)*. *Huisgen*'s "sextet limiting formula" *(C)*[3] suggests that such compounds are potential starting materials for 1,4-dipolar cycloadditions[3]. Since five-membered mesoionic heterocycles can, in many cases, be used for 1,3-dipolar cycloadditions[4] to give five-membered ring systems, the mesomeric six-membered ring betaines *(1)* ought to be suitable for 1,4-dipolar cycloadditions leading to six-membered heterocycles.

This is in fact shown to be the case in the reaction of *(1)* with dimethyl acetylenedicarboxylate *(2)* and maleic anhydride *(3)*[5]. Thus, *(1a)* and *(1b)* react with *(2)* with loss of phenyl isocyanate to give, respectively, the 2-pyridones *(5a)* and *(5b)* in good yields. As in the case of the analogous reactions with acetylene derivatives[4, 5] the tendency to rearomatization leads to elimination of a neutral molecule (in this case $C_6H_5N{=}C{=}O$) from the primary addition product *(4)*.

(1a), R = H; *(1b)*, R = $CH_2C_6H_5$



In the reaction of *(1b)* with maleic anhydride, however, we have been able to isolate the 1:1 adduct *(6)*[6]. The structure of *(6)* has been confirmed by mass spectrometry, molecular weight determination (528), and NMR spectroscopy (in DMSO). The NMR spectrum contains one singlet at δ = 3.70 due to the methylene protons of the benzyl group, two doublets of the *cis*-protons in positions 7 and 8 at δ = 4.32 and 5.53, $J = 9.5$ Hz, as well as signals for 20 aromatic protons at δ = 6.8—8.8. The IR spectrum (in KBr) with anhydride bands at 1860 and 1790 cm^{-1} and C=O bands at 1710 and 1670 cm^{-1}, is also in agreement with this structure.

2-Pyridones (5a) and (5b)

The solutions of *(1a)* and *(1b)* (5 mmol) in chlorobenzene (25 ml) are heated under reflux with *(2)* (1.4 ml. 10 mmol) for 16 h. The residue recovered after evaporation under vacuum is digested with petroleum ether. *(5a)*: yield 83%, colorless needles recrystallized from methanol, m. p. 168—170 °C[7]; free dicarboxylic acid (by hydrolysis with 1 N NaOH): m. p. 253—256 °C[7]. *(5b)*: yield 67%, colorless needles recrystallized from ethanol, m. p. 235—237 °C[7].

4-Benzyl-3,5-dioxo-1,2,6-triphenyl-2,6-diazabicyclo[2.2.2]-octane-7,8-dicarboxylic anhydride (6)

(1b) (1.07 g, 2.5 mmol) and *(3)* (0.25 g, 2.5 mmol) are vigorously ground together and then heated at 170 °C for

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15 min. After digestion of the melt with cyclohexane and recrystallization from chlorobenzene, compound *(6)*, m. p. 231—233 °C, was obtained in 61% yield[7].

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[1] Mesionic Malonyl Heterocycles, Part 2.—Part 1: [2].

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[4] For summaries see: *M. Ohta* and *H. Kato* in *J. P. Snyder*: Nonbenzoid Aromatics. Academic Press, New York 1969, p. 117 ff.; *R. Huisgen* in "Aromaticity", Chem. Soc. Spec. Publ. No. *21*, London 1967, p. 51.

[5] Analogous reactions of the bicyclic "*anhydro*-2-hydroxyl-1-methyl-4-oxopyrido[1,2-*a*]pyrimidinium hydroxide" with acetylenedicarboxylate derivatives have been described recently by *K. T. Potts* and *M. Storm*, J. Org. Chem. *36*, 8 (1971).

[6] The reason for adducts such as *(6)* being difficult to isolate is that if R = H in compound *(1)* only "ene-addition" occurs, as observed by *Potts* [5] in the reaction of zwitterions with tetracyanoethylene or azodicarboxylate. We have found that the addition is also hindered—for electronic, and particularly steric reasons—if *(1)* contains a substituent such as C_6H_5.

[7] The structures of the products were confirmed by elemental analysis (C, H, N) and IR and NMR spectroscopy.

Preferred *syn*-Elimination from *trans*-1,2-Dichloro- and *trans*-1,2-Dibromocyclodecane[**]

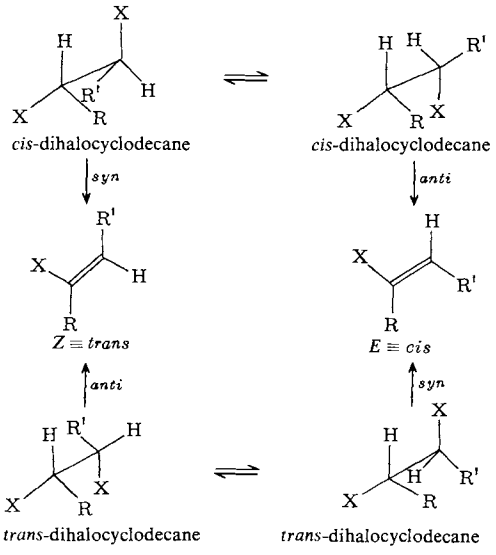
By *Jiří Sicher*, *Gérald Jan*, and *Manfred Schlosser*[*]

The mechanisms of elimination of hydrogen bromide from secondary alkyl bromides and from cycloalkyl bromides of medium ring size differ significantly[1].

A detailed discussion of these divergencies is only possible if one can differentiate between the four elementary elimination processes *syn* → *cis*, *syn* → *trans*, *anti* → *cis*, and *anti* → *trans*[2]. Keeping this in mind we have extended our investigations to *vic*-dihaloalkanes[3] and 1,2-dihalocyclodecanes. Such substrates exist in two diastereoisomeric forms, for each of which two of the stereochemical pathways are blocked: 1-halo-*trans*-cyclodecene (*Z* isomer) can arise from *cis*-1,2-dihalocyclodecane only by *syn* elimination, and from the *trans* isomer by *anti* elimination. Conversely, the 1-halo-*cis*-cyclodecene (*E* isomer) must be formed from the *cis*-dihalide by *anti*-coplanar elimination and from the *trans*-dihalide by *syn*-coplanar elimination (Scheme 1).

Cyclodecane derivatives have been chosen as cyclic model compounds since their elimination behavior differs most typically from that of acyclic substrates. Furthermore, the heats of formation of the configurational isomers of 1,2-dihalocyclodecanes and especially those of the configurational isomers of 1-halocyclodecenes should be very similar, so that differences in reactivity due to differences in thermodynamic stability (Polanyi-Hammond principle!) should be negligible.

trans-1,2-Dichlorocyclodecane was readily prepared from *cis*-cyclodecene and trichloroamine[4], and *trans*-1,2-dibromocyclodecane by addition of bromine to *cis*-cyclodecene in ethanol-free carbon tetrachloride at −10 °C[5, 6]. Unfortunately, we have not yet been able to prepare the *cis*-dihalides[7]; however, the results obtained on treating the *trans* isomers with bases and observations from earlier work[8] already permit a first comparison of the dehydrohalogenation mechanisms of ten-membered cyclic dihalides with those of the corresponding acyclic substrates.



Scheme 1. Elimination pathways open to *cis*- and *trans*-1,2-dihalocyclodecanes. R,R′ = —$(CH_2)_8$—.

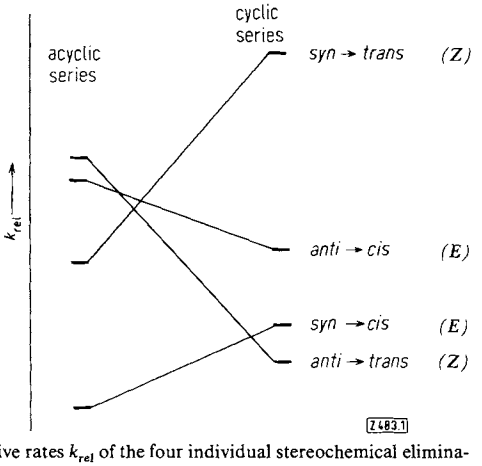


Figure. Relative rates k_{rel} of the four individual stereochemical elimination processes which can take part in the base-induced dehydrohalogenation of acyclic substrates (haloalkane → *cis*- and *trans*-alkene; *vic*-dihaloalkane → *Z*- and *E*-1-haloalkene; see left-hand side of figure) and cyclic substrates (halocyclodecane → *cis*- and *trans*-cyclodecene; *vic*-dihalocyclodecane → *Z*- and *E*-1-halocyclodecene; see right-hand side of figure). Base/solvent system: potassium butoxide in *tert*-butyl alcohol.

As can be seen from the above figure, going from the acyclic series to the cyclodecane derivative—at least in *tert*-butyl alcohol—always favors *syn*-coplanar cleavage, and particularly the *syn* → *trans* process. Evidently, the transition states profit from the reduction in transannular repulsive forces. On the other hand *anti* elimination is considerably retarded in the ten-membered ring system. In addition to steric hindrance of attack by bases[1], steric hindrance of halogen solvation may play an important role here too.

The most striking consequence of this situation is the cross-over of *syn* → *cis* and *anti* → *trans* reactivities. In the case of the ten-membered ring system, the *anti* → *trans* route, most favored with acyclic substrates, falls back to

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last place behind the exceptionally enhanced *syn* → *cis* elimination. The *cis* isomer, which is the product of a *syn* elimination, always predominates (see Table).

Table. Dehydrohalogenation of *trans*-1,2-dihalocyclodecane to *cis*- and *trans*-1-halocyclodecene.

Base/solvent system	Halogen = Cl			Halogen = Br		
	cis:*trans* [a]	Reaction conditions	Yield (%) [b]	*cis*:*trans* [a]	Reaction conditions	Yield (%) [b]
Piperidine	7.7:1	48 h, 135 °C	96	5.3:1	6 h, 100 °C	100
$NaOC_2H_5/HOC_2H_5$	5.6:1	16 h, 100 °C	53	4.7:1	20 min, 80 °C [c]	97
$KOC(CH_3)_3/HOC(CH_3)_3$	10 :1	1 h, 100 °C	68	12 :1	30 min, 90 °C	95
$KOC(CH_3)_3$/Benzene	20 :1	1 h, 100 °C	95	23 :1	30 min, 90 °C	95

[a] The product ratios were determined by vapor phase chromatography (2.5 m 5% SE 30, 120 °C and 2.5 m 20% Carbowax 1540) from the peak areas (no correction was made for substance-dependent differences in detector response). For identification, the 1-halocyclodecenes were isolated, spectroscopically examined, submitted to combustion analysis, and reduced to *cis*- or *trans*-cyclodecenes with sodium in liquid ammonia. The by-products were identified by comparison of their retention times with those of independently prepared reference substances: 3-chloro-*cis*-cyclodecene, 2—25% [b] (from 2-cyclodecen-1-ol and thionyl chloride, 62%, b.p. 55—57 °C/0.2 torr); 3-bromo-*cis*-cyclodecene, 3—5% [b] (from *cis*-cyclodecene and *N*-bromosuccinimide [9], 67% b.p. 56—57 °C/0.05 torr); 8—24% [b] *cis*- and *trans*-3-ethoxycyclodecene (from 3-bromo-*cis*-cyclodecene and ethanol in the presence of sodium ethoxide, 72%, b.p. 99—101 °C/torr). On the basis of observed retention times, the remaining by-products formed could be 3-chloro-*trans*-cyclodecene (1—14% [b]) and $C_{10}H_{16}$ hydrocarbons (1—16% [b]).

[b] The yields are corrected for unchanged material (*i.e.* net yields). Under the chosen conditions, 14% (in *tert*-butyl alcohol solution)—83% (in benzene solution) of the *trans*-1,2-dichlorocyclodecane was converted and generally about 70% of the *trans*-1,2-dibromocyclodecene.

[c] 10% KOH instead of $NaOC_2H_5$ in ethanol.

The ease of conversion *via* the two possible stereochemical pathways appears to be very much less dependent on the base/solvent system than the *syn* → *trans* process in the dehydrobromination of cyclodecyl bromide[9]. Both the relative and the absolute rates of dehydrohalogenation change only slightly upon variation of the solvent.

Received: July 29, 1971 [Z 483 IE]
German version: Angew. Chem. *83*, 1012 (1971)

[1] For a review see: *J. Sicher*, Angew. Chem. *84* (1972), in press.

[2] Cf. *M. Svoboda, J. Závada*, and *J. Sicher*, Collect. Czech. Chem. Commun. *33*, 1415 (1968); *J. Závada, M. Svoboda*, and *J. Sicher, ibid. 33*, 4027 (1968); *J. Sicher, J. Závada*, and *M. Pánková*, Chem. Commun. *1968*, 1147.

[3] *J. Sicher* and *E. Byrne*, to be published.

[4] Method: *K. W. Field* and *P. Kovacic*, Synthesis *1969*, 135.

[5] By-product: 4% *cis*-1,6-dibromocyclodecane.

[6] Cf. *M. Havel, M. Svoboda*, and *J. Sicher*, Collect. Czech. Chem. Commun. *34*, 340 (1969).—The carbon tetrachloride used at that time contained small amounts of ethanol.

[7] The compound, m.p. 84.5—86.5 °C, obtained by *J. G. Traynham* and *D. B. Stone* [J. Org. Chem. *35*, 2027 (1970)] is definitely *not cis*-1,2-dichlorocyclodecane but rather a cyclic sulfite.

[8] *J. Závada, J. Krupička*, and *J. Sicher*, Collect. Czech. Chem. Commun. *33*, 1393 (1968).

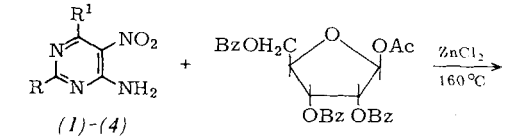
[9] Cf. *A. T. Blomquist, R. E. Burge*, and *A. C. Sucsy*, J. Amer. Chem. Soc. *74*, 3636 (1952).

Synthesis of 8-Ribofuranosyl- and 2-Ribofuranosylamino-7-oxo-7,8-dihydropteridines[**]

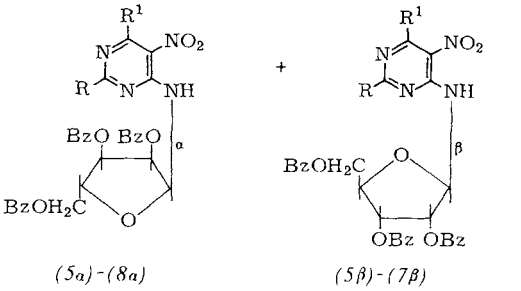
By *Dieter Autenrieth, Helmut Schmid, Klaus Harzer, Manfred Ott*, and *Wolfgang Pfleiderer*[*]

We have recently shown that the fusion of 4-amino-5-nitropyrimidines with fully acylated ribofuranose derivatives[2] is a decisive step in the synthesis of pteridine *N*-8-ribofuranosides[1].

To test the scope of this method we have carried out analogous reactions on the pyrimidines *(1)*—*(3)* using various substituents in positions 2 and 6. The results showed that ribosidation of the 4-amino group with simultaneous formation of the anomeric 5-nitro-4α- and -4β-ribofuranosylaminopyrimidines *(5)*—*(7)* takes place, as expected, in the presence of aprotic substituents such as halogen, alkoxy, alkylthio, or dialkylamino. The anomeric mixture



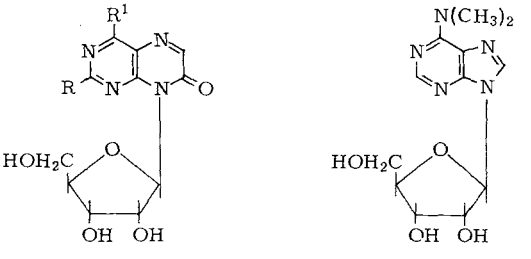
(1)-*(4)*



(5α)-*(8α)* *(5β)*-*(7β)*

(6), (7) → *(9), (10)*

(8) → *(11)* + *(12)*



(9)-*(11)* *(12)*

	R	R^1
(1), (5)	Cl	Cl
(2), (6), (9)	OCH_3	OCH_3
(3), (7), (10)	SCH_3	$N(CH_3)_2$
(4), (8), (11)	H	$N(CH_3)_2$

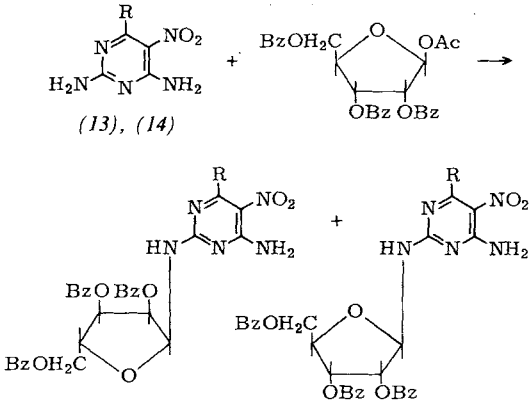
[*] Dr. D. Autenrieth, Dr. H. Schmid, Dr. K. Harzer, Dr. M. Ott, and Prof. Dr. W. Pfleiderer
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[(7), 29% yield] obtained from 4-amino-6-dimethylamino-2-methylthio-5-nitropyrimidine (3) was resolved into its components by preparative layer chromatography; the α/β ratio proved to be 2:1, the same as in previous investigations[2].

Absence of a substituent in position 2 is to be avoided since this usually leads to lower yields; thus reaction of 4-amino-2-dimethylamino-5-nitropyrimidine (4) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose gives a reaction product in 10% yield only. Interestingly, according to NMR investigations the product is exclusively pure α-riboside (8).

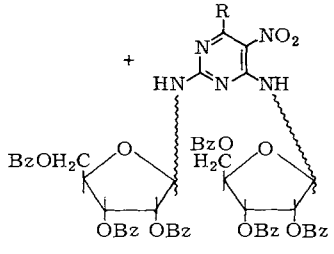
Conversion into the corresponding 7-oxo-7,8-dihydropteridine *N*-8-riboside was accompanied by the usual difficulties; relatively good yields of the desired product, after reduction of the nitro group and subsequent cyclization by condensation with glyoxylate hemiacetal, were obtained only in the conversions of (6)—(8) into (9) to (11) (23, 13, and 20% resp.). The isolated products were exclusively β-ribosides, irrespective of the nature of the glycosidic linkage of the starting material. The isolation and identification of 6-dimethylamino-9-β-D-ribofuranosylpurine (12)[3], which is formed alongside (11) probably by nucleophilic addition of the 4-amino function to the azomethine grouping of the initially-formed Schiff base and subsequent hydrolysis, decarboxylation and dehydrogenation, threw some light on the possible side reactions that take place. On fusion of 2,4-diamino-5-nitropyrimidines (13) and (14) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose reaction occurs almost exclusively at the 2-amino group and affords the chromatographically separable anomeric mixtures (15) and (16), respectively, as main products. Small amounts of the corresponding 2,4-bis(ribosylamino) derivatives (17) and (18), which also usually occur as mixtures of the four possible pairs of anomers (2α, 4α; 2α 4β; 2β 4α; 2β 4β), are formed as side products. In the case of 2,4-bis(2,3,5-tri-*O*-benzoyl-D-ribofuranosylamino)-6-dimethylamino-5-nitropyrimidine (17) we were able to separate the four components by very carefully planned layer chromatography; the structure and configuration of the anomers were then determined by NMR, and ORD and CD spectroscopy.



(13), (14)

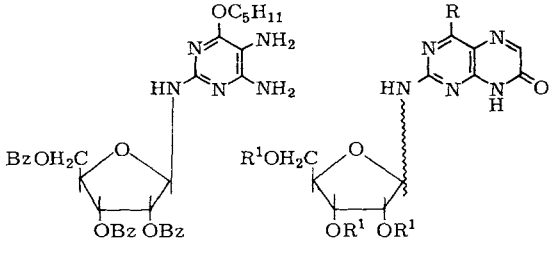
(15α), (16α) 27% 22%

(15β), (16β) 22% 23%



(17), (18)
1.5% 5.4%

	R	R^1
(13), (15), (17), (20)	$N(CH_3)_2$	C_6H_5CO
(14), (16), (18), (21)	OC_5H_{11}	H
(22)	OC_5H_{11}	CH_3CO



(19) (20)-(22)

(15α) → (20α) + (20β)
(15β) → (20α) + (20β)
(16) → (19) → (21) → (22)

Reduction with Raney nickel/H_2 and subsequent condensation with glyoxylate in methanol led, both in the case of pure (15α) as well as (15β), to partial anomerization of the glycosidic linkage, since the two anomeric 2-ribosylamino-7-oxo-7,8-dihydropteridine derivatives (20α) and (20β) were obtained in different amounts in each case [from (15α), 11% (20α) and 22% (20β); from (15β), 3.5% (20α) and 1.5% (20β)]. Sodium dithionite reduction proves to be very satisfactory in the case of the anomeric mixture (16) since the 5-amino base (19) can be isolated. Condensation with glyoxylate to the Schiff base and alkoxide-catalyzed cyclization leads, with simultaneous deacylation, to the α, β mixture (21) (25% yield), which is just as difficult to separate into pure components as its acetylation mixture (22% yield).

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German version: Angew. Chem. 83, 970 (1970)

[1] *H. Rokos* and *W. Pfleiderer*, Chem. Ber. *104*, 770 (1971).
[2] *H. Rokos* and *W. Pfleiderer*, Chem. Ber. *104*, 748 (1971).
[3] *B. R. Baker* and *J. P. Joseph*, J. Amer. Chem. Soc. *77*, 15 (1955).

General Synthesis of Pteridine *N*-8-Glycosides[**]

By *Wolfgang Pfleiderer*, *Dieter Autenrieth*, and *Margarete Schranner*[*]

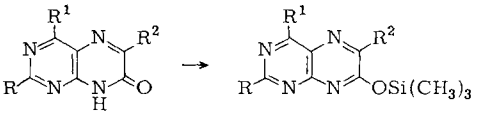
The relatively difficult accessibility of pteridine *N*-8-glycosides *via* 4-glycosylamino-5-nitropyrimidines[1] induced us to attempt direct *N*-glycosidation of the pteridine system by the same method as has been used with success in the case of 2-oxo-1,2-dihydroquinoxalines[2]. This is based on the Birkofer variant[3] of the Hilbert-Johnson synthesis[4] which recently has been used with great success, partic-

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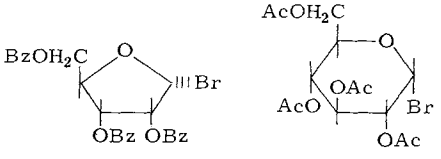
ularly in the pyrimidine nucleoside series[5, 6] and in related nitrogen heterocycles[7].

The 7-oxo-7,8-dihydropteridines *(1)*—*(4)* were used as starting materials; these were first silylated with hexamethyldisilazane to the corresponding 7-trimethylsilyloxy derivatives *(5)*—*(8)* and then converted into the halogenoses *(9)*, *(10)*, and *(11)*. Here, the "Wittenburg conditions"[5]—prolonged (several hours) boiling in benzene in the presence of $HgO/HgBr_2$ (Table)—proved most satisfactory and generally applicable.

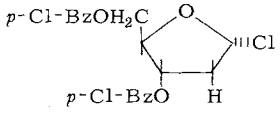


(1) - (4) *(5) - (8)*

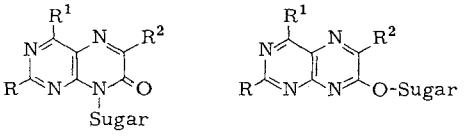
	R	R^1	R^2
(1), (5)	H	H	H
(2), (6)	$(CH_3)_2N$	H	H
(3), (7)	$(CH_3)_2N$	H	CH_3
(4)	NH_2	$(CH_3)_2N$	H
(8)	$(CH_3)_3SiNH$	$(CH_3)_2N$	H



(9) *(10)*



(11)



(12) - (25) *(17a), (18a)*

In the reactions of *(5)* with *(9)* and *(10)*, *N*-8-glycosidation takes place to give 7-oxo-7,8-pteridine *N*-8-(2,3,5-tri-*O* benzoyl-β-D-ribofuranoside) *(12)* and -*N*-8-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside) *(13)* respectively. The reaction of *(6)* and *(8)* with *(9)* are sterically controlled[8] and lead to *N*-8-β-D-ribosides *(14)* and *(15)* respectively, whereas the expected *N*-8-α,β-anomeric mixture *(16)* was obtained from *(6)* and *(11)*. With α-acetobromoglucose *(10)*, a mixture of isomers *(17)* and *(17a)* was obtained (66% yield), which could be resolved into its pure components only by very tedious layer chromatography giving low recoveries. The same difficulty in separation of components was encountered in the case of the mixture of isomers *(18)* and *(18a)* formed in an analogous fashion in 77% yield by reaction of *(7)* with *(9)*. A further, interesting reaction was observed to take place between *(8)* and *(9)* in acetonitrile in absence of catalyst at room temperature: A mixture of anomers *(19)* and *(15)* was

[1] *W. Pfleiderer* and *E. Bühler*, Chem. Ber. *99*, 3022 (1966); *H. Rokos* and *W. Pfleiderer*, *ibid. 104*, 748, 770 (1971); *D. Autenrieth*, *H. Schmid*, *K. Harzer*, *M. Ott*, and *W. Pfleiderer*, Angew. Chem. *83*, 970 (1971); Angew. Chem. internat. Edit. *10*, 927 (1971).

[2] *W. Pfleiderer* and *M. Schranner*, Chem. Ber. *104*, 1915 (1971).

[3] *L. Birkofer*, *A. Ritter*, and *H. P. Kühltau*, Chem. Ber. *97*, 934 (1964); *L. Birkofer* and *A. Ritter*, Angew. Chem. *77*, 414 (1965); Angew. Chem. internat. Edit. *4*, 417 (1965).

[4] *G. E. Hilbert* and *T. B. Johnson*, J. Amer. Chem. Soc. *52*, 4489 (1930); *J. Pliml* and *M. Prystas*, Advan. Heterocycl. Chem. *8*, 115 (1967).

[5] *E. Wittenburg*, Chem. Ber. *101*, 1095, 1614 (1968).

[6] *U. Niedballa* and *H. Vorbrüggen*, Angew. Chem. *82*, 449 (1970); Angew. Chem. internat. Edit. *9*, 461 (1970); *H. Vorbrüggen* and *U. Niedballa*, Tetrahedron Lett. *1970*, 3571; *M. W. Winkley* and *R. K. Robins*, J. Chem. Soc. *C 1969*, 791; *M. W. Winkley*, *ibid. C 1970*, 1365.

[7] *G. R. Revankar* and *L. B. Townsend*, J. Heterocycl. Chem. *5*, 785 (1968); *R. L. Tolman*, *G. L. Tolman*, *R. K. Robins*, and *L. B. Townsend*, *ibid. 7*, 799 (1970); *J. T. Witkowski* and *R. K. Robins*, J. Org. Chem. *35*, 2635 (1970); *B. L. Currie*, *R. K. Robins*, and *M. J. Robins*, J. Heterocycl. Chem. *7*, 323 (1970); *B. L. Currie*, *M. J. Robins*, and *R. K. Robins*, *ibid. 8*, 221 (1971); *M. W. Winkley*, *G. F. Judo*, and *R. K. Robins*, *ibid. 8*, 237 (1971).

[8] *H. G. Fletcher*, Trans. New. York. Acad. Sci. Ser. II, *30*, 649 (1968).

[9] *G. Zemplén*, *A. Geres*, and *J. Hadacsy*, Ber. dtsch. chem. Ges. *69*, 1827 (1936).

Table. Data for compounds *(12)* to *(25)*, and *(17a)* and *(18a)*. Unless otherwise stated *(12)* to *(19)* were obtained according to [5] and *(20)* to *(25)* according to [9].

Reaction	Yield (%) [a]	M.p. (°C)	R	R^1	R^2	Sugar residue
(5)+(9)→(12)	41	78–90 [b]	H	H	H	1-β-*(9)*
(5)+(10)→(13)	7.5	182–186	H	H	H	1-β-*(10)*
(6)+(9)→(14)	49	174–177	$(CH_3)_2N$	H	H	1-β-*(9)*
(8)+(9)→(15)	36	93–99 [b]	NH_2	$(CH_3)_2N$	H	1-β-*(9)*
(6)+(11)→(16)	7.5	81–93 [b]	$(CH_3)_2N$	H	H	1-α,β-*(11)*
(6)+(10)→(17)	2	184–190	$(CH_3)_2N$	H	H	1-β-*(10)*
+(17a)	3	98–110 [b]	$(CH_3)_2N$	H	H	1-β-*(10)*
(7)+(9)→(18)	5	[b]	$(CH_3)_2N$	H	CH_3	1-β-*(9)*
+(18a)	8	114–117	$(CH_3)_2N$	H	CH_3	1-β-*(9)*
(8)+(9)→(19) [c]	4	83–92 [b]	NH_2	$(CH_3)_2N$	H	1-α-*(9)*
(14)→(20)	59	195–198	$(CH_3)_2N$	H	H	1-β-D-ribofuranosyl
(16)→(21)	39	172–174	$(CH_3)_2N$	H	H	1-α,β-D-2-deoxyribofuranosyl
(17)+(17a)→(22)	57	133–155	$(CH_3)_2N$	H	H	1-β-D-glucopyranosyl
(18)+(18a)→(23)	20	186–188	$(CH_3)_2N$	H	CH_3	1-β-D-ribofuranosyl
(15)→(24)	75	233 (dec.)	NH_2	$(CH_3)_2N$	H	1-β-D-ribofuranosyl
(19)→(25)	43	203	NH_2	$(CH_3)_2N$	H	1-α-D-ribofuranosyl

[a] Yields based on pure isolated compounds.
[b] Amorphous.
[c] Without catalyst at room temperature in acetonitrile; *(15)* is also formed.

obtained which could be separated by preparative layer chromatography into its components in 4 and 16% yield respectively.

The free *N*-8-glycosides *(20)*—*(25)* (Table) can usually be obtained in good yields by deacylation with sodium methoxide according to *Zemplén*'s method[9] in which the *O,N*-isomeric mixtures can also be used for their preparation because of retro-cleavage of the 7-*O*-glycosides into the initial pteridines. The structures of the products synthesized were confirmed by comparison of UV spectra with those of the corresponding *N*-8-methyl and 7-methoxypteridines; the configuration of the glycosidic bond was established by NMR spectroscopic investigation.

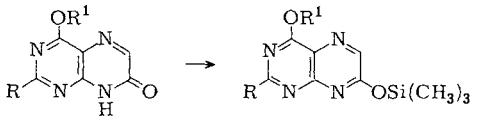
Received: August 24, 1971 [Z 494b IE]
German version: Angew. Chem. *83*, 971 (1971)

Synthesis of Isoxanthopterin *N*-8-β-D-Ribofuranoside—A Structural Analog of Guanosine[**]

By *Helmut Schmid, Margarete Schranner,* and *Wolfgang Pfleiderer*[*]

The successful direct *N*-8-glycosidation[1] of 7-oxo-7,8-dihydropteridines by the "silyl method" made it fitting to undertake the synthesis also of isoxanthopterin *N*-8-β-D-ribofuranoside *(29)*, a structural analog of guanosine. With this aim in mind we have investigated the behavior of the 2-amino-4-alkoxy-7,8-dihydropteridines *(1)*—*(6)* in the form of their trimethylsilyl derivatives *(8)*—*(13)* toward 1-bromo-2,3,5-tri-*O*-benzoyl-D-ribofuranose *(15)*.

The completely blocked 2-dimethylamino-4-methoxy-7-oxo-7,8-dihydropteridine *(1)* reacts with hexamethyldisilazane to give the 7-trimethylsilyloxy derivative *(8)* which, on boiling in benzene in the presence of $HgO/HgBr_2$ catalyst, affords a mixture of *N*-8-*(17)* (56%) and 7-*O*-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside) *(17a)* (7%). The



(1)-*(7)* *(8)*-*(14)*

	R	R^1		R	R^1
(1)	$(CH_3)_2N$	CH_3	*(8)*	$(CH_3)_2N$	CH_3
(2)	NH_2	CH_3	*(9)*	$(CH_3)_3SiNH$	CH_3
(3)	NH_2	$CH(CH_3)_2$	*(10)*	$(CH_3)_3SiNH$	$CH(CH_3)_2$
(4)	NH_2	C_5H_{11}	*(11)*	$(CH_3)_3SiNH$	C_5H_{11}
(5)	NH_2	$CH_2C_6H_5$	*(12)*	$(CH_3)_3SiNH$	$CH_2C_6H_5$
(6)	CH_3CONH	C_5H_{11}	*(13)*	CH_3CONH	C_5H_{11}
(7)	NH_2	H	*(14)*	$(CH_3)_3SiNH$	$(CH_3)_3Si$

bis(trimethylsilyl) derivatives *(9)*—*(12)* behave similarly. The isomers obtained were separated by layer- or column chromatography on silica gel (Table).

Further reaction products that can be separated are the diribosides of type *(30)*, to which we tentatively assign the given structures on the basis of the fact that they lose a ribose residue when treated with methoxide.

The "Vorbrüggen conditions"[2] can also be used in this series: thus, reaction of *(9)* with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose *(16)* in acetonitrile in the presence of $SnCl_4$ gives *(18)* in 24% yield. As in *(6)*, acylation at the 2-amino group affords protection of this function against silylation as well as against glycosidation. Compound *(22)* can be obtained from *(13)* in 10% yield.

In the silylation of the isoxanthopterin *(7)* the amine group and the two amide functions enter into reaction and the tris(trimethylsilyl) derivative *(14)*, which can be distilled under high vacuum, is formed. In the ribosidation of *(14)* a complex mixture of substances is formed which can be separated chromatographically into two clean fractions. The main fraction (54% yield) contains an extraordinarily difficultly separable mixture of *N*-8- *(23)* and 7-*O*-riboside *(23a)* and the second fraction small amounts (4%) of an isoxanthopterin tririboside whose structure is presumably that of *(24)*. Because of the alkali-lability of the *O*-glycosidic and the exocyclic *N*-glycosidic linkages, compound *(24)*

Table. Data for the compounds *(17)* to *(29)*, and *(17a)* to *(21a)* and *(23a)*. R^3 = 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl.

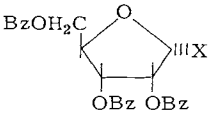
Reaction	Yield (%)	M.p. (°C)	R	R^1	R^2
(8) + *(15)* → *(17)*	56	84–92 [a]	$(CH_3)_2N$	CH_3	C_6H_5CO
+ *(17a)*	7	167	$(CH_3)_2N$	CH_3	C_6H_5CO
(9) + *(15)* → *(18)*	20	104–112 [a]	NH_2	CH_3	C_6H_5CO
+ *(18a)*	22	104–112 [a]	NH_2	CH_3	C_6H_5CO
(10) + *(15)* → *(19)*			NH_2	$CH(CH_3)_2$	C_6H_5CO
+ *(19a)*	24	98–106 [a]	NH_2	$CH(CH_3)_2$	C_6H_5CO
(11) + *(15)* → *(20)*	14	84–92 [a]	NH_2	C_5H_{11}	C_6H_5CO
+ *(20a)*	6	72–81 [a]	NH_2	C_5H_{11}	C_6H_5CO
(12) + *(15)* → *(21)*	14	193–194	NH_2	$CH_2C_6H_5$	C_6H_5CO
+ *(21a)*	10	98–107	NH_2	$CH_2C_6H_5$	C_6H_5CO
(13) + *(15)* → *(22)*	10	61–70 [a]	CH_3CONH	C_5H_{11}	C_6H_5CO
(14) + *(15)* → *(23)*			NH_2	H	C_6H_5CO
+ *(23a)*			NH_2	H	C_6H_5CO
+ *(24)*	4	45–52 [a]	R^3NH	R^3	C_6H_5CO
(21) → *(25)*	83	257	NH_2	H	C_6H_5CO
(17) + *(17a)* → *(26)*	60	192	$(CH_3)_2N$	CH_3	H
(18) + *(18a)* → *(27)*	25	260 (dec.)	NH_2	CH_3	H
(19) + *(19a)* → *(28)*	20	224	NH_2	$CH(CH_3)_2$	H
(23) + *(23a)* + *(24)* → *(29)*	23	>300	NH_2	H	H

[a] Amorphous.

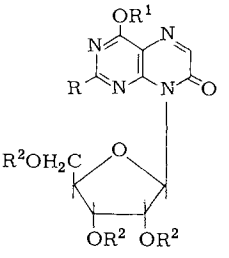
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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

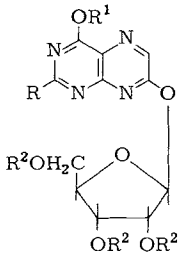
can, like the isomeric mixture *(23)* and *(23a)*, be converted into the free isoxanthopterin *N*-8-β-D-ribofuranoside *(29)* by treatment with methoxide. Compound *(29)* is also obtained when *(21)* is debenzylated catalytically with Pd/H_2 to *(25)* and then *(25)* subsequently debenzoylated.



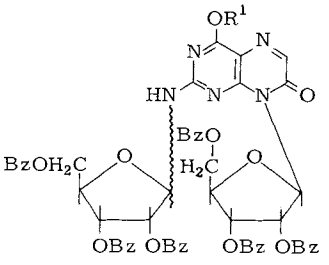
(15), X = Br
(16), X = $OCOCH_3$



(17)-*(29)*



(17a)-*(21a)*, *(23a)*



(30)

In the treatment of *(21)* with methoxide, substitution of the benzyloxy by a methoxy group to form *(27)* takes place at the same time as deacylation. No other anomalous reactions have been observed in conversion of blocked derivatives into free *N*-8-ribosides *(26)*—*(29)*. The structure and configuration of the glycosidic linkage in each of the substances were established and confirmed by UV and NMR spectroscopy.

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[1] *W. Pfleiderer, D. Autenrieth,* and *M. Schranner*, Angew. Chem. *83*, 971 (1971); Angew. Chem. internat. Edit. *10*, 928 (1971).

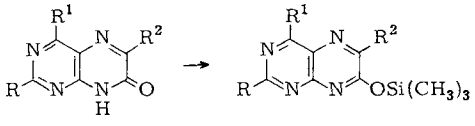
[2] *U. Niedballa* and *H. Vorbrüggen*, Angew. Chem. *82*, 449 (1970); Angew. Chem. internat. Edit. *9*, 561 (1970).

Synthesis of 4-Amino-7-oxo-7,8-dihydropteridine *N*-8-β-D-Ribosides—Structural Analogs of Adenosine[**]

By *Manfred Ott* and *Wolfgang Pfleiderer*[*]

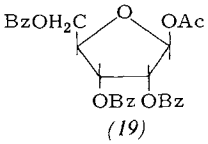
In our studies on the direct glycosidation of 7-oxo-7,8-dihydropteridines by the "silyl method" we have established that the conditions chosen for the reaction of 7-trimethylsilyloxypteridine with halogenoses in boiling benzene in the presence of Hg salts as catalyst[1] do not generally lead to optimum yields of desired product. In particular, the absence of electron-donating substituents in position 2 leads to low yields of *N*-8-ribosides. For example, 2-dimethylamino-7-trimethylsilyloxypteridine *(17)*[2] affords the desired product in 49% yield, the isomeric 4-dimethylamino derivative *(10)*, on the other hand, in only 27%. The desired *N*-8 riboside *(21)* can be obtained using 4-amino-7-oxo-7,8-dihydropteridin *(2)* as starting material; the bis(trimethylsilyl) derivative *(11)* of *(2)* is prepared first and then subjected to the corresponding reaction conditions—a route that was previously not possible.

A satisfactory variant has proved to be the combined "Silyl-fusion" method in which the 7-trimethylsilyloxypteridines *(10)*—*(18)* are allowed to react with a fully acylated sugar [1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose *(19)*] in the presence of a Lewis acid (preferably $ZnCl_2$) at 140—170°C (see Table).

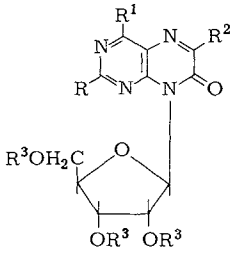


(1)-*(9)* → *(10)*-*(18)*

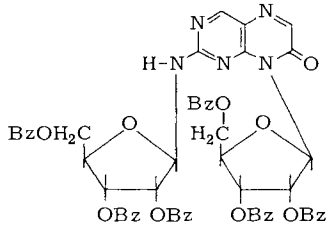
	R	R^1	R^2
(1)	H	$(CH_3)_2N$	H
(2)	H	NH_2	H
(3)	CH_3S	$(CH_3)_2N$	H
(4)	CH_3S	NH_2	H
(5)	CH_3S	NH_2	$CO_2C_2H_5$
(6)	$C_6H_5CH_2S$	NH_2	$CO_2C_2H_5$
(7)	CH_3S	NH_2	CO_2CH_3
(8)	$N(CH_3)_2$	H	H
(9)	NH_2	H	H
(10)	H	$(CH_3)_2N$	H
(11)	H	$(CH_3)_3SiNH$	H
(12)	CH_3S	$(CH_3)_2N$	H
(13)	CH_3S	$(CH_3)_3SiNH$	H
(14)	CH_3S	$(CH_3)_3SiNH$	$CO_2C_2H_5$
(15)	$C_6H_5CH_2S$	$(CH_3)_3SiNH$	$CO_2C_2H_5$
(16)	CH_3S	$(CH_3)_3SiNH$	CO_2CH_3
(17)	$(CH_3)_2N$	H	H
(18)	$(CH_3)_3SiNH$	H	H



(19)



(20)-*(34)*



(35)

In this way *(11)* gives the riboside *(21)* in 18% yield, and subsequent debenzoylation converts *(21)* into the structural analog of adenosine, 4-amino-7-oxo-7,8-dihydropteridine *N*-8-β-D-ribofuranoside *(30)*. As expected, the presence of 2-alkylthio substituents favors the reaction; the mono- or bis(trimethylsilyl) derivatives *(12)*—*(16)* of the 4-amino-7-oxo-7,8-dihydropteridines *(3)*—*(7)* react smoothly and undergo preferred *N*-8-ribosidation with steric control of the glycosidic linkage of aglycon and sugar residue[3] to give the β-ribosides *(22)*—*(26)*. Interestingly,

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it has also been established that reactions in acetonitrile at room temperature in presence of $SnCl_4$—under the conditions preferred by *Vorbrüggen*[4] in the pyrimidine series—offer no direct advantages; *e. g.* the yield of *(26)* from *(16)* and *(19)* is likewise 54%. The potential of the described fusion method is illustrated very well by the reaction of *(17)* with *(19)* in which ribosidation at *N*-8 takes place and *(27)* is formed in almost quantitative yield. In the reaction of *(18)* with *(19)*, difficulties were encountered in the working up; a diriboside of probable structure *(35)* was isolated (4.5%) in addition to the main product *(28)* (21%).

Table. Data for compounds *(20)* to *(34)*.

Reaction	R	R^1	R^2	R^3	Yield (%)	Fp (°C)
(10)+*(19)*→*(20)*	H	$(CH_3)_2N$	H	C_6H_5CO	27	168–170
(11)+*(19)*→*(21)*	H	NH_2	H	C_6H_5CO	16	95–110 [a]
(12)+*(19)*→*(22)*	CH_3S	$(CH_3)_2N$	H	C_6H_5CO	52	80–100 [a]
(13)+*(19)*→*(23)*	CH_3S	NH_2	H	C_6H_5CO	75	100–110 [a]
(14)+*(19)*→*(24)*	CH_3S	NH_2	$CO_2C_2H_5$	C_6H_5CO	60	106
(15)+*(19)*→*(25)*	$C_6H_5CH_2S$	NH_2	$CO_2C_2H_5$	C_6H_5CO	23	187–188
(16)+*(19)*→*(26)*	CH_3S	NH_2	CO_2CH_3	C_6H_5CO	54	102–110
(17)+*(19)*→*(27)*	$(CH_3)_2N$	H	H	C_6H_5CO	96	175–177
(18)+*(19)*→*(28)* [b]	NH_2	H	H	C_6H_5CO	21	95–103 [a]
(20)→*(29)*	H	$(CH_3)_2N$	H	H	54	158–160
(21)→*(30)*	H	NH_2	H	H	43	120–125
(22)→*(31)*	CH_3S	$(CH_3)_2N$	H	H	62	182
(23)→*(32)*	CH_3S	NH_2	H	H	86	203–205
(26)→*(33)*	CH_3S	NH_2	CO_2CH_3	H	28	144–146
(28)→*(34)*	NH_2	H	H	H	75	253

[a] Amorphous.
[b] Alongside 4.5% *(35)*.

Preparation of the unprotected pteridine *N*-8-β-D-ribofuranosides *(29)*—*(34)* could usually be realized quite successfully by way of Zemplén hydrolysis[5]. The given structure and configurations of the glycosidic linkage were established and confirmed by UV and NMR spectroscopy.

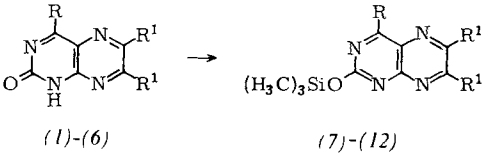
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[1] *E. Wittenburg*, Chem. Ber. *101*, 1095 (1968).
[2] *W. Pfleiderer, D. Autenrieth*, and *M. Schranner*, Angew. Chem. *83*, 971 (1971); Angew. Chem. internat. Edit. *10*, 928 (1971).
[3] *H. G. Fletcher*, Trans. New York Acad. Sci. Ser. II, *30*, 649 (1968).
[4] *U. Niedballa* and *H. Vorbrüggen*, Angew. Chem. *82*, 449 (1970); Angew. Chem. internat. Edit. *9*, 461 (1970).
[5] *G. Zemplén, H. Geres*, and *J. Hadacsy*, Ber. dtsch. chem. Ges. *69*, 1827 (1936).

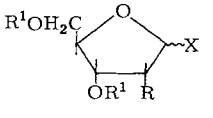
Synthesis of Lumazine and Isopterin *N*-1-β-D-Ribofuranosides and -(2-Deoxyribofuranosides)—Structural Analogs of Uridine, Cytidine, and Thymidine[**]

By *Götz Ritzmann, Klaus Harzer*, and *Wolfgang Pfleiderer*[*]

Amide functions in heterocyclic nitrogen ring systems are potential reaction centers for glycosidation and since *N*-8 substitution has recently proved possible in 7-oxo-7,8-dihydropteridines[1], an analogous reaction has been tried with lumazine *(1)* and isopterin *(5)* and their derivatives, particularly on use of the Hilbert-Johnson-Birkofer method[2]. To obtain the structural analogs of the pyrimidine nucleosides uridine, cytidine, and thymidine in the pteridine series, the starting substances *(1)*—*(6)* were first silylated with hexamethyldisilazane to give the compounds *(7)*—*(12)*, which were then allowed to react with the halogenoses *(13)* and *(14)* in boiling benzene in the presence of $HgO/HgBr_2$[3]. Under the chosen reaction conditions, lumazine *(1)* and isopterin *(5)* and their 6,7-dimethyl and 6,7-diphenyl derivatives undergo preferred glycosidation at *N*-1.



(1)-(6) *(7)-(12)*



(13), (14)

	R	R^1
(1)	OH	H
(2)	OH	CH_3
(3)	OH	C_6H_5
(4)	$N(CH_3)_2$	H
(5)	NH_2	H
(6)	NH_2	C_6H_5

	R	R^1
(7)	$(CH_3)_3SiO$	H
(8)	$(CH_3)_3SiO$	CH_3
(9)	$(CH_3)_3SiO$	C_6H_5
(10)	$N(CH_3)_2$	H
(11)	$(CH_3)_3SiNH$	H
(12)	$(CH_3)_3SiNH$	C_6H_5

	X	R	R^1
(13)	Br	C_6H_5COO	C_6H_5CO
(14)	Cl	H	$p\text{-}CH_3C_6H_4CO$

The 2,4-bis(trimethylsilyloxy)pteridines *(7)*, *(8)*, and *(9)* react with *(13)* to give mixtures which can be separated by column chromatography into their components, *viz.* the *N*-1-β-D-ribofuranosides *(15)*—*(17)* (as main products) and the lumazine 1,3-diribosides *(15a)*—*(17a)* (as secondary products). The isopterin derivatives *(10)*—*(12)* react

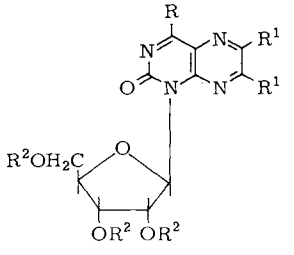
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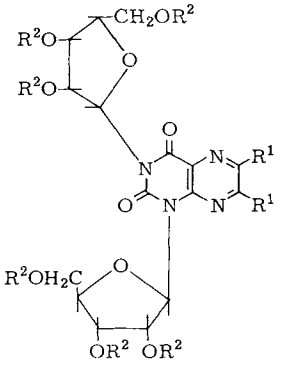
Table 1. Data for compounds *(15)* to *(28)*.

Reaction	R	R^1	R^2	Yield (%)	M.p. (°C)
(7)+(13)→(15)	OH	H	C_6H_5CO	50	[a]
+(15a)		H	C_6H_5CO	3.2	127–128
(8)+(13)→(16)	OH	CH_3	C_6H_5CO	44	120
+(16a)		CH_3	C_6H_5CO	2.9	[a]
(9)+(13)→(17)	OH	C_6H_5	C_6H_5CO	74	145–155
+(17a)		C_6H_5	C_6H_5CO	1	172–173
(10)+(13)→(18)	$N(CH_3)_2$	H	C_6H_5CO	65	103 [a]
(11)+(13)→(19)	NH_2	H	C_6H_5CO	49	105–120 [a]
(12)+(13)→(20)	NH_2	C_6H_5	C_6H_5CO	39	198
(15)→(21)	OH	H	H	73	182–184
(16)→(22)	OH	CH_3	H	71	204
(17)→(23)	OH	C_6H_5	H	78	234–236
(17a)→(23a)		C_6H_5	H	19	172–175
(18)→(24)	$N(CH_3)_2$	H	H	80	186
(19)→(25)	NH_2	H	H	75	148
(20)→(26)	NH_2	C_6H_5	H	77	252
(27) [b]		C_6H_5	C_6H_5CO	7.5	[a]
(27)→(28)		C_6H_5	H	12	168–172

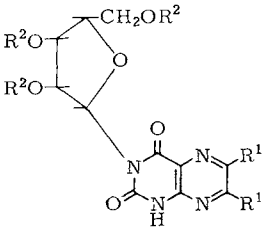
[a] Amorphous.
[b] Formation, see text.



(15)-(26)



(15a)-(17a), (23a)



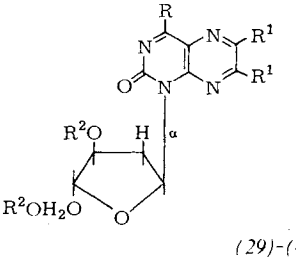
(27), (28)

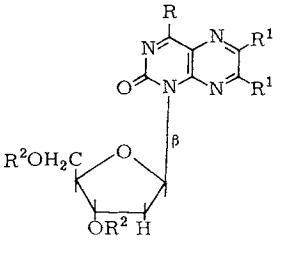
in a corresponding fashion, with substitution at *N*-1 to give the compounds *(18)—(20)* (Table 1).

Reaction of *(9)* with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane at room temperature in presence of $SnCl_4$ leads to *(17)* and *(17a)*, each in 20% yield, and, as a further reaction product, lumazine *N*-3-β-D-ribofuranoside *(27)*. The free pteridine ribosides *(21)—(26)*, *(23a)*, and *(28)* were prepared *via* the well-known method of deacylation with sodium methoxide or methanolic ammonia. It was found that when the latter reagent is employed for the deacylation of *(18)* not only hydrolysis of benzoyl groups takes place but also replacement of the 4-dimethylamino group by $-NH_2$ (Table 1).

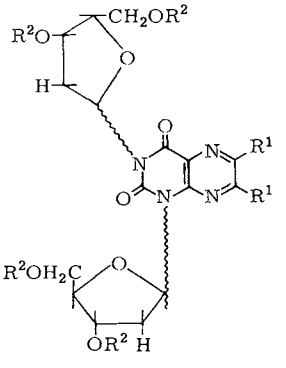
In principle, the lumazine and isopterin (2-deoxyribosides) (Table 2) can be prepared by the same method, if the silylated pteridine derivatives are treated in the usual way with 1-chloro-3,5-di-*p*-toluoyl(2-deoxy-D-ribofuranose) *(14)*. As expected, complex reaction mixtures are formed which can be resolved into their components on a preparative scale only by tedious column and layer chromatographic separations. We have also been able to establish that product distribution in this series largely depends on the reaction conditions. In almost all cases, the main fractions consist of *N*-1-(deoxyribosides) in the form of anomeric mixtures. Further separation leads to isolation of pure α- and β-anomers, the α-anomer always being the dominant component. Structural assignment can be carried out on the basis of NMR spectral findings.

In the lumazine series a 1,3-bis-(2-deoxyriboside) fraction [*(30a), (32a), (34a)*] can be separated, albeit in small amounts, as a second, more mobile reaction product, which according to chromatographic investigations might be a preparatively inseparable mixture of the four possible combinations of anomers (α,α; α,β; β,α, and β,β).

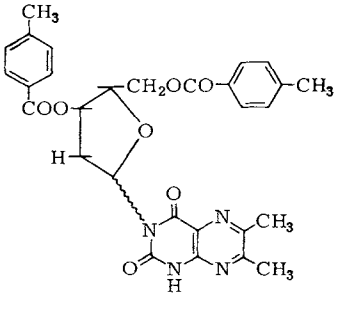




(29)-(44)



(30a), (32a), (34a)



(45), (46)

Table 2. Data for compounds *(29)* to *(46)*.

Reaction		R	R^1	R^2	Yield (%)	M.p. (°C)
(7) + *(14)* → *(29)*	α	OH	H	p-$CH_3C_6H_4CO$	17	156–158
+ *(30)*	β	OH	H	p-$CH_3C_6H_4CO$	5.3	[a]
+ *(30a)*			H	p-$CH_3C_6H_4CO$	2.8	[a]
(8) + *(14)* → *(31)*	α	OH	CH_3	p-$CH_3C_6H_4CO$	23	154–155
+ *(32)*	β	OH	CH_3	p-$CH_3C_6H_4CO$	8.2	[a]
+ *(32a)*			CH_3	p-$CH_3C_6H_4CO$	5	[a]
(9) + *(14)* → *(33)*	α	OH	C_6H_5	p-$CH_3C_6H_4CO$	29	185–190
+ *(34)*	β	OH	C_6H_5	p-$CH_3C_6H_4CO$	12	155–160
+ *(34a)*			C_6H_5	p-$CH_3C_6H_4CO$		[a]
(11) + *(14)* → *(35)*	α	NH_2	H	p-$CH_3C_6H_4CO$	18	132
+ *(36)*	β	NH_2	H	p-$CH_3C_6H_4CO$	6.6	127
(29) → *(37)*	α	OH	H	H	77	145 (dec.)
(30) → *(38)*	β	OH	H	H	32	155 (dec.)
(31) → *(39)*	α	OH	CH_3	H	75	180 (dec.)
(32) → *(40)*	β	OH	CH_3	H	71	160 (dec.)
(33) → *(41)*	α	OH	C_6H_5	H	61	189–191
(34) → *(42)*	β	OH	C_6H_5	H	90	160 (dec.)
(35) → *(43)*	α	NH_2	H	H	65	200 (dec.)
(36) → *(44)*	β	NH_2	H	H	60	200 (dec.)
(45) [b]	α				1.6	156–157
(46) [b]	β				0.6	[a]

[a] Amorphous.
[b] Formation, see text.

On reacting *(8)* with *(14)* we obtained, in addition to *(31)*, *(32)*, and *(32a)*, the isomeric *N*-3-mono(2-deoxy-D-riboside) mixture of *(45)* and *(46)*. Deacylation to the free lumazine and isopterin *N*-1-(2-deoxy-D-ribofuranosides) *(37)*—*(44)* was carried out by Zemplén hydrolysis[4] and usually gave good yields of the desired product.

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[1] *W. Pfleiderer, D. Autenrieth*, and *M. Schranner*, Angew. Chem. *83*, 971 (1971); Angew. Chem. internat. Edit. *10*, 928 (1971).

[2] *L. Birkofer, A. Ritter*, and *H. P. Kühltau*, Chem. Ber. *97*, 934 (1964).

[3] *E. Wittenburg*, Chem. Ber. *101*, 1095 (1968).

[4] *G. Zemplén, H. Geres*, and *J. Hadacsy*, Ber. dtsch. chem. Ges. *69*, 1827 (1936).

Atomic Reactions with Carbonylmetal Compounds[**]

By *Karl H. Becker* and *Maria Schürgers*[*]

Carbonylmetal compounds react rapidly in the gaseous phase at low pressure with oxygen, hydrogen, or nitrogen atoms to give electronically excited products which emit characteristic spectra.

Because of their reactivity carbonylmetal compounds play a significant role as catalysts in oxidation processes in polluted atmospheres; for example, the oxidation of NO to NO_2 is accelerated considerably if slight amounts of $Fe(CO)_5$ are present[1]. The presence of trace amounts of carbonylmetal compounds in hydrocarbon-air mixtures leads to either quenching of the hydrocarbon-air flames or, at least, to substantial reduction of their flame velocities[2]; as a consequence of this, $Fe(CO)_5$ can be employed as an antiknock agent in gasolines[3].

We have investigated the reactions of $Cr(CO)_6$, $Mo(CO)_6$, $W(CO)_6$, $Fe(CO)_5$, and $Ni(CO)_4$ with oxygen, hydrogen, and nitrogen atoms. The atoms were generated in a microwave discharge and then mixed with the carbonylmetal compounds in a reaction chamber. The total pressure in the reaction chamber was a few torr, the partial pressure of the carbonylmetal compounds 10^{-6} torr at a flow rate of 3 l/s.

The chemiluminescence observed in the reactions was recorded with a spectral resolution of about $\Delta\lambda = 10$ Å by a detector arrangement consisting of a 1.5 m Czerny-Turner monochromator and an EMI-9665-B photomultiplier.

Inspection of the spectra permits the following conclusions to be drawn:

1. In reactions of carbonylmetals with oxygen atoms an apparently continuous emission occurs which must be assigned to a polyatomic emitter.
2. MO* emissions occur in all reactions of the type $M(CO)_n + O$ except $Mo(CO)_6 + O$.
3. Emissions of excited, neutral metal atoms M* are identifiable in the spectra of reactions $M(CO)_n + O$ as well as in those of the reactions $M(CO)_n + H$ and $M(CO)_n + N$.
4. In the reactions $Mo(CO)_6 + H$ and $Mo(CO)_6 + N$ an intense band system is observed at 5200 Å which is emitted by a diatomic molecule.

On the basis of reaction kinetics and spectroscopic data, the continuum can be interpreted as emission from MCO*. That the emissions occurring in all the reactions of carbonyl metals with oxygen were due to CO_2^* could be ruled out because of the different low wavelength limits between 3000 Å and 4000 Å.

MO* emissions are possibly due to direct formation of this species from oxygen atoms and metal atoms. Metal atoms are formed from carbonylmetal compounds by stepwise degradation of the CO ligand with formation of CO_2.

An explanation for the occurrence of metal atom emission lines in all the reactions is that the metals do not lose, or only partly lose, their valence energy, which they possess as central atom in the carbonylmetal compounds, and thus remain in an excited state. This assumption is supported by the fact that (i) the same M* emission lines occur in reactions of a carbonylmetal compound with different atoms, and (ii) the excitation energies of the atoms observed,

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Cr*, Mo*, W*, and Fe*, are always less than the corresponding valence energy. A spectral analysis of the band system, which, in the case of reactions $Mo(CO)_6 + H$ and $Mo(CO)_6 + N$, occurs at 5200 Å, indicates the presence of a diatomic species having a very low bonding energy of about 1.5 kcal/mol; quadratic dependence of the intensity of emission on the $Mo(CO)_6$ concentration suggests that this system is to be assigned to an excited, weakly bound Mo_2^* species.

The rate constants for the overall reaction $M(CO)_n +$ atoms → products were determined in a flow tube at a linear flow velocity of 10 m/s. The intensity of chemiluminescence, which follows a first order reaction in the presence of excess atoms served as indicator. The rate constants of the light reaction $M(CO)_n + O$ were obtained by comparison with the standard reaction $NO + O \rightarrow NO_2 + h\nu$[4]. All the rate constants are listed in Table 1.

Table 1. Rate constants in [l. mol^{-1} s^{-1}]; $T = 298$ K.

$M(CO)_n$	Overall reaction			Light reaction
	H atoms	N atoms	O atoms	O atoms
$Cr(CO)_6$	—	4.0×10^{8}	4.2×10^{9}	1.5×10^{7}
$Mo(CO)_6$	3.0×10^{8}	2.9×10^{8}	1.9×10^{9}	1.9×10^{7}
$W(CO)_6$	—	5.5×10^{8}	1.7×10^{9}	3.8×10^{7}
$Fe(CO)_5$	—	—	—	5.8×10^{7}

Comparison of the rate constants of the overall reaction $M(CO)_n + O \rightarrow$ products with those of the light reaction $M(CO)_n + O$ shows that a small percentage of the overall reaction leads to formation of excited products.

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Pulse Fourier Transform ^{13}C-NMR Spectroscopy of Mutarotating Sugars[**]

By *Wolfgang Voelter, Eberhard Breitmaier,* and *Günther Jung*[*]

Routine measurement of the mutarotation of sugars by ^{13}C-NMR spectroscopy has until now been hindered by fundamental and instrumental difficulties[1, 2]: Although the sensitivity of ^{13}C resonance, which is relatively very much lower than that of ^{1}H resonance, can be improved by accumulation of spectra with averaging computers (CAT method, Computer Averaged Transitions), the unusually long accumulation times required are often unacceptable. Consequently, only the spectra of mutarotated anomeric mixtures could be obtained hitherto by conventional ^{13}C-NMR spectroscopy. Development of the new, more sensitive and more rapid recording technique known as Pulse Fourier Transform (PFT) NMR spectroscopy has now made it also possible to study time-dependent phenomena such as mutarotation by means of ^{13}C resonance. Furthermore, the recording of the ^{1}H broad-band decoupling ^{13}C spectra of reducing sugars before and after mutarotation equilibrium has greatly extended the scope of the previously used methods of ^{13}C signal assignment (comparison of the resonances with those of other compounds, and off-resonance decoupling[1, 2]) in the investigation of carbohydrates.

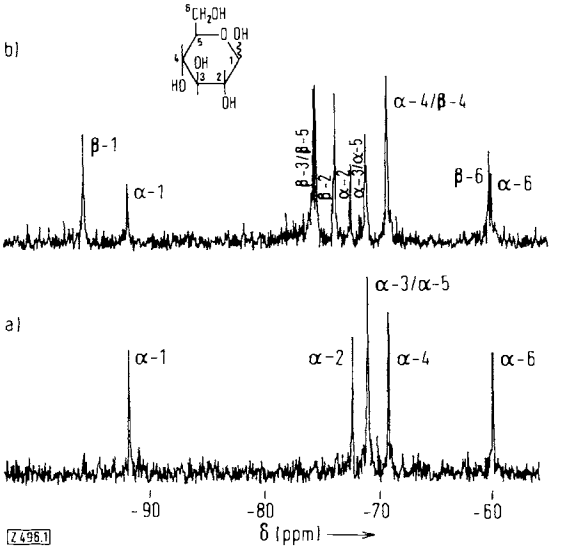


Fig. 1. PFT ^{13}C-NMR spectra of D-glucose, 0.5 M in D_2O, 512 pulses, pulse interval 0.8 s; a) immediately, b) three days after preparation of solution (ppm values negative w.r.t. TMS external = 0).

The spectrum of α-D-glucose (Fig. 1a) shows five signals. After adjustment of the mutarotation equilibrium ten signals can be recognized (Fig. 1b) ([2]: eight signals). The assignments of most signals are well known. The signal at −95.70 ppm is ascribed to C-1 of the β-anomer (equatorial hydroxyl group) on the basis of the known downfield shift[1-5] of about 4 ppm compared to that of C-1 of the α-anomer (axial hydroxyl group). The assignment of β-C-3/β-C-5[2] (Table) arises since the signals of the γ carbon atoms C-3 and C-5 are displaced to lower fields than the signal of the β carbon C-2 when the axial hydroxyl group on C-1 changes into an equatorial position. Comparison of the Figures 1a and 1b reveals that the crystalline D-glucose used by us was present as the α-anomer.

D-Trehalose is formed by glycosydic coupling of two α-D-glucose residues. The influence of the glycosidic linkage ought to be the least at C-4 and C-6; the ppm-values of the signals of these carbon atoms are almost the same as those of the corresponding carbon atoms of α-D-glucose (Table). In the disaccharide the signal of the anomeric carbon atom (C-1) is displaced downfield by about 1.15 ppm from the corresponding signal of α-D-glucose. Such downfield shifts have also been established in the comparison of signals of a free sugar with those of its methylglycoside[2-4]. Since the difference of the chemical shifts of C-2 of α-methyl-D-glucopyranoside and C-2 of α-methyl-D-glucose is less than 0.5 ppm, the C-2 (2') signal of trehalose (−72.35 ppm) can be compared with the C-2 resonance of α-D-glucose (−72.55 ppm). The signals at −70.85 and −71.90 then belong to C-3 (3') and C-5 (5').

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Table. ^{13}C-shifts of D-glucose and disaccharide in D_2O (ppm-values negative w.r.t. TMS external = 0 ppm).

C-Atom	Cellobiose	Glucose [a]	Trehalose [b]	Maltose
β-6	− 59.75	−60.40	−60.35	−60.60
α-6	− 59.95	−60.60		−60.45
6′	− 60.45			−60.35
4′	− 69.25			−69.15
α-3/α-5	− 69.90	−71.25	−70.85	−69.80
α-3/α-5	− 71.05		−71.90	−71.15
α-2	− 71.20	−72.55	−72.35	−71.50
2′	− 73.00			−73.85
β-2	− 73.75	−73.90		−73.00
β-3/β-5	− 74.10	−75.55		−74.40
β-3/β-5	− 74.60	−75.70		−76.00
3′/5′	− 75.35			−72.50
3′/5′	− 75.80			−72.70
β-4	− 78.50	−69.40		−76.60
α-4	− 78.60		−69.50	−76.85
α-1	− 91.65	−91.85	−93.00	−91.65
β-1	− 95.55	−95.70		−95.60
1′	−102.40			−99.35

[a] See Fig. 1.
[b] The corresponding C atoms of both glucose residues gave the same signals (only one entered here).

The ^{13}C-spectra of the disaccharides cellobiose and maltose were assigned by comparison with the spectra of trehalose and D-glucose before and after adjustment of the mutarotation equilibrium (Table).

The signals of the coupling atoms C-4 of maltose (−76.60/76.85) and cellobiose (−78.60/78.50), as expected, appear downfield from that of the C-4 signal of D-glucose (−69.40). The signals of the carbon atoms C-2, C-3, and C-5 are assigned on the basis of the 1,3-diaxial interaction (see above) in glucose residues containing an α axial group. In the case of glucose residues having α anomeric C-atoms the signal sequence downfield is C-3/C-5, C-2 and for those with β anomeric C-atoms C-2, C-3/C-5.

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Simple Synthesis of Hexafluoro Complexes of Osmium(IV), Iridium(IV), and Platinum(IV)

By *Wilhelm Preetz* and *Yukhanneh Petros*[*]

Hexafluoro complexes of the heavy tetravalent platinum metals have been known for more than fifty years[1, 2]; however, their preparation by methods previously given in the literature and in text books[3, 4] always meets with difficulties since simple complexes have to be reacted with elemental fluorine or very reactive compounds that can be obtained only by reaction with free fluorine, *e.g.* BrF_3. In such reactions hexafluoro complexes of pentavalent platinum metals are first formed which are readily reduced in alkaline solution to the corresponding complexes with a quadrivalent central atom. They can, however, be prepared directly in a KHF_2 melt without the use of aggressive reagents:

$$K_2[MX_6] + 6KHF_2 \longrightarrow K_2[MF_6] + 6KF + 6HX\uparrow$$
(M = Os, Ir, Pt; X = Cl, Br, I)

Since the heavier halogen hydrides, unlike HF, do not form stable solvates and are immediately liberated from fused salts at relatively high temperatures, complete conversion is usually achieved. $K_2[PtBr_6]$, which is very stable, reacts slowly; increased temperatures favor reaction, but simultaneous decomposition of KHF_2 takes place rapidly above 350 °C with liberation of HF and the $K_2[PtF_6]$ formed decomposes pyrolytically. This is avoided by use of $K_2[PtCl_6]$.

The yield and purity of the compound prepared is determined by the water content of the starting material: the drier the starting substance the lower the amount of by-products formed (presumably oxygen-bridged polynuclear complexes). Since hexafluoro complexes are very stable in aqueous solution they are readily purified by recrystallization. By-products formed in the preparation of osmium complexes are readily removed hydrolytically by gentle warming in alkaline solution. $K_2[IrF_6]$, which has frequently been described as a red or pink complex, can be prepared in the pure state by continuous ionophoresis[5, 6]; like other hexafluoro complexes it is only pale yellow in color. Although the red impurity normally present (maximum 2%) has a very low ionic mobility its complete removal, either by partial hydrolysis or by precipitation, has not been achieved.

The IR spectra of the pure hexagonal Cs complexes are all very similar. The new method for preparing hexafluoro complexes of the heavy platinum metals considerably simplifies the route previously described by *Seel*[7] for the purely chemical winning of free fluorine.

Experimental:

K_2MX_6 (0.5 g) is intimately mixed with very dry (heated for one week at 120 °C), finely divided KHF_2 and heated in a nickel crucible (300—400 °C) until a clear, almost colorless melt with escaping gas bubbles is obtained.

Immediately crystals start to separate out, the melt is quenched and the fine, yellow (M = Os, Pt) or red (M = Ir) cake is extracted two or three times with a few ml of cold water to remove KHF_2. The hexafluoro complex is then extracted from the residue with warm water (80 °C); on cooling the extract, the complex is obtained as hexagonal platelets in 60—80 °C yield.

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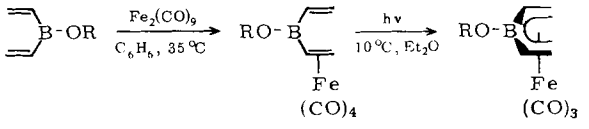
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Benzyloxydivinylboranetricarbonyliron—A π-Divinylborane Complex Containing a Boron—Iron Bond[**]

By *Gerhard E. Herberich* and *Horst Müller*[*]

The discovery of complexes of the aromatic borine ("borabenzene", C_5H_5B)[1-3], in which boron fully participates in the metal-ligand bond[1,4,5] led us to investigate the possible existence of complexes of analogous non-cyclic B—C ligand systems. In this paper we wish to report the first complex with a divinylborane derivative as a π-ligand.

Alkoxydivinylboranes[6] *(1)* react with $Fe_2(CO)_9$ in benzene to give labile tetracarbonyliron complexes *(2)* having one free and one complexed vinyl group. Removal of the $Fe(CO)_5$ formed and subsequent irradiation leads to alkoxydivinylboranetricarbonyliron *(3)*:



(1) *(2)* *(3)*

(a), R = n-C_4H_9; *(b)*, R = $C_6H_5CH_2$

This two-step reaction was first established in the case of the butyl series (a) using NMR and IR spectroscopy. The analogous benzyloxydivinylboranetricarbonyliron *(3b)* of the benzyl series (b) was then prepared in analytically pure form [38% yield (based on $Fe_2(CO)_9$); orange oil, very sensitive to air, crystallizable from *n*-pentane at −60 °C; soluble without decomposition in pentane, benzene, ether, and acetone].

The mass spectrum[7] (50 eV) of *(3b)* contains, in addition to the molecular ion $LFe(CO)_3^+$ [L = *(1b)*] (I_{rel} = 4), the following fragment ions: $LFe(CO)_2^+$ (5), $LFe(CO)^+$ (12), LFe^+ (63), $FeC_9H_{10}^+$ (100), $FeC_7H_8^+$ (48), $C_7H_7^+$ (50), Fe^+ (42). Successive loss of the CO groups, of CH_2=CH—BO, C_2H_2, and C_7H_8 is proved by metastable peaks at *m/e* 258.5, 230.7, 203.1, 132.8, 125.9, and 21.2.

The IR spectrum shows three sharp, very intense ν_{CO} bands (in hexane) at 2050, 1998, and 1986 cm^{-1}, as are typical for tricarbonyliron complexes with strong perturbation of the local C_{3v} symmetry of the $Fe(CO)_3$ group[8].

In the ^{1}H-NMR spectrum of *(3b)* (Table) the signals of the vinyl groups show *trans-* and *cis*-couplings of 14.5 and 12.0 Hz, while the geminal coupling can not be observed, as usual in the case of terminal methylene groups of π-ligands[9]. All the resonances can be assigned on the basis of these couplings and of the relative intensities. The large differences between the chemical shifts of $H_{(1)}$, H_{syn}, and H_{anti} should be noted. Such differences are generally observed in the case of allyl and butadiene[9], as well as pentadienyl[10] ligands. Thus, in the case of $[Fe(CO)_3(C_5H_7)]ClO_4$ the corresponding signals of H_2[11], H_{syn}, and H_{anti} occur in the same sequence and with similar shift differences; they are shifted about 2—3 ppm downfield, merely because of the charge on the cation and the different solvent. Accordingly, the ligand *(1b)* is bound to the metal as a pentadienyl and not as a non-conjugated diene[12]: the metal-to-ligand bond includes a boron-iron bond.

Table. ^{1}H-NMR spectrum of *(3b)* in C_6D_6 (60 MHz; 20 °C).

Signal	$I_{rel.}$	τ [a]	Multiplicity and coupling constants in Hz
C_6H_5	(5) [b]	3.2–3.5	m
CH_2	2	5.57	s
$H_{(1)}$	2	6.80 (3.74) [c]	dd } $\lvert J_{1,syn}\rvert$ = 12.0 (9.8)
H_{syn}	2	8.37 (6.25)	d } $\lvert J_{1,anti}\rvert$ = 14.5 (13.0)
H_{anti}	2	9.77 (7.83)	d } $\lvert J_{syn,anti}\rvert$ < 1 (3.5)

[a] Measured against external TMS; [b] partially overlapped by solvent signal; [c] in brackets, corresponding value of spectrum of $[Fe(CO)_3(C_5H_7)]ClO_4$ in SO_2, cf. [10].

Experimental:

A solution of *(1b)* in benzene (35 ml), prepared as described by *Matteson*[6] from 2,2-divinyl-1,3,2-oxazaborinane (1.5 g, 12 mmol), is stirred with $Fe_2(CO)_9$ (2.18 g, 6.0 mmol) at 35 °C, under rigorous exclusion of O_2. After one hour the reaction mixture is filtered and all volatiles are removed by evaporation (0.1 torr). The residue is then taken up in ether (50 ml) and irradiated for 7 hours [mercury vapor lamp (70 W), Duran glass vessel, cooling with water (10 °C)]. Removal of the ether and distillation under high vacuum at 65—75 °C affords an orange oil; in order to remove residual benzyl alcohol this oil is dissolved in pentane, filtered through a small amount of Al_2O_3, and redistilled. The resulting product is recrystallized three times from pentane (3 × 5 ml) at −60 °C discarding the mother liquor. Finally it is dried under vacuum at 0 °C. Yield of *(3b)*: 0.71 g.

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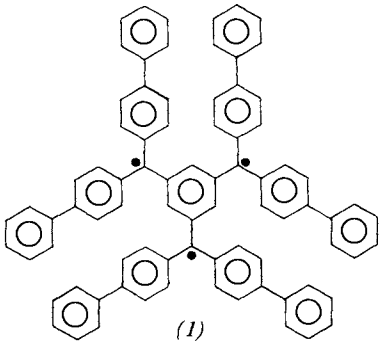
[12] With the signals of all vinyl protons within *ca.* 1 ppm. Cf. $[Fe(CO)_3(CH_2{=}CH)_2Si(CH_3)_2]$: *T. W. Fitch* and *H. E. Herbold,* Inorg. Chem. *9*, 1926 (1970).

1,3,5-Benzenetriyltris[di(*p*-biphenyl)methyl], a Radical Having a Quartet Ground State that Dimerizes by Entropy Bonding

By *Gerd Kothe, Ernst Ohmes, Jürgen Brickmann,* and *Herbert Zimmermann*[*]

Organic radicals having three unpaired electrons (three-spin systems) have only been known for a few years. Their magnetic properties are determined by dipole- and exchange interactions of the radical electrons[1-9].

In the case of weak magnetic dipole coupling three-spin systems give ESR spectra with hyperfine structure. Strong coupling, however, leads to broad unstructured ESR signals. Little is known about the magnetic properties of these radicals. In no case has a zero field splitting been observed so far. In the present communication we report the results of investigations on the hydrocarbon *(1)*, a three spin system with strong magnetic dipole coupling.



(1)

The synthesis of the reddish brown, oxygen-sensitive radical *(1)* has been described previously[4]. Preliminary molecular-weight determinations indicated that in benzene radical (1) is partly associated[4]. In order to determine the nature of this association the dependence of the average molecular weight $\bar{M}$ on the sample concentration c_0 referred to monomeric *(1)* in benzene was measured. Values of $\bar{M}$ between 1750 and 1920 ($M_{\text{monomer}} = 1030$) were found for concentrations c_0 between 3.5×10^{-3} and 3.3×10^{-2} mol/l. This finding suggests dimerization of *(1)*.

We have also established the dimerization equilibrium

$$2(1) \rightleftharpoons (1)_2$$

by ESR spectroscopy from the dependence of the molar paramagnetic susceptibility on the concentration c_0. The experimental technique employed has been described elsewhere[10]. A plot of the ratio of the measured molar paramagnetic susceptibility χ of toluene solutions referred to c_0 to the molar susceptibility χ_s of a free monoradical, which serves as standard, *versus* c_0 is shown in Figure 1. χ/χ_s falls rapidly with increasing c_0 and reaches a value corresponding to only about 15% of the susceptibility of the monoradical at the highest concentration investigated. It appears that association involves spin coupling with formation of diamagnetic dimer $(1)_2$.

The value of χ/χ_s increases sharply with falling c_0. At the lowest measureable concentrations c_0 the ratio χ/χ_s

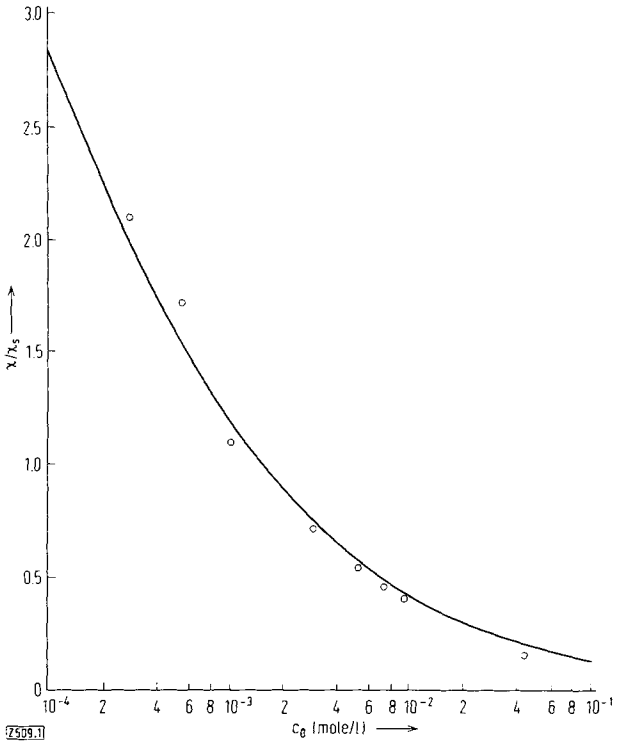


Fig. 1. Concentration dependence of the relative paramagnetic susceptibility χ/χ_s in toluene solution. χ = measured molar paramagnetic susceptibility; χ_s = molar paramagnetic susceptibility of a standard (DPPH); c_0 = concentration of sample, based on monomeric *(1)*; $T = 263$ K, o = experimental point, —— = calculated curve.

assumes values exceeding twice the susceptibility of a monoradical. Thus the three-spin system *(1)* can exist in limiting cases either as a triradical $\chi_{(1)} = 3\chi_s$, or as a quartet state, $\chi_{(1)} = 5\chi_s$. For both possible limiting forms, the association constant

$$K = \frac{c_{(1)_2}}{c_{(1)}^2} = \frac{1-(\chi/\chi_{(1)})}{2c_0(\chi/\chi_{(1)})^2} \qquad (1)$$

was calculated from the concentration dependence of the measured susceptibility χ.

The value of the equilibrium constant remains constant within the limits of experimental accuracy over the whole concentration range of two orders of magnitude only for $\chi_{(1)} = 5\chi_s$. At 263 K the value of K is $(6.7 \pm 0.3) \times 10^3$ l/mol. The curve in Figure 1 was calculated with this equilibrium constant from eq. (1). The agreement achieved is satisfactory. The radical *(1)* therefore possesses a quartet ground state and is in equilibrium with a diamagnetic dimer.

The temperature dependence of K, which can also be measured by ESR spectroscopy, permits calculation of the standard enthalpy of association ΔH^0. Figure 2 shows a plot of log K *versus* $1/T$. The slope of the curve shows that within the limits of accuracy the enthalpy of association is $\Delta H^0 = 0$. This result is surprising since association equilibria are generally temperature dependent. The equilibrium constant gives a standard free energy of association of $\Delta G^0 = -4.6$ kcal/mol and a standard entropy of association of $\Delta S^0 = +17.6$ e. u., both at 263 K.

The dimer $(1)_2$ has a singlet ground state. The simplest interpretation for this fact is an associate in which two

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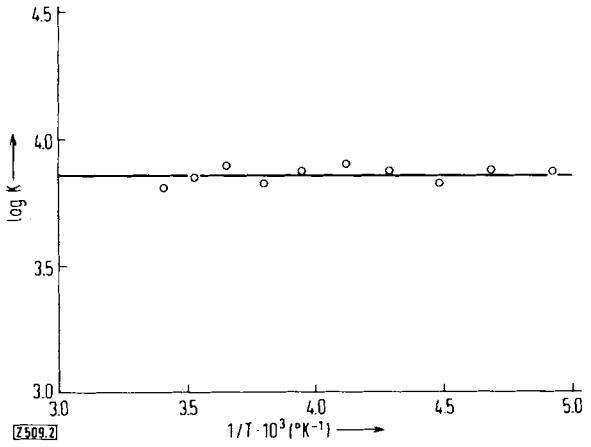


Fig. 2. Temperature dependence of the association constant K of *(1)* in toluene. $c_o = 9.9 \times 10^{-4}$ mol/l.

molecules of *(1)* are bound by way of three σ bonds with spin coupling. However, this possibility appears rather unlikely since an association *via* σ bonds is hardly compatible with a bonding enthalpy $\Delta H^0 = 0$; moreover, steric considerations also contraindicate the formation of three σ bonds in the complex. Regardless of the question of the structure of the dimer and the mechanism of the spin coupling we wish to emphasize that association occurs only as a result of an increase in the entropy of the entire system: It would appear that we are here confronted with a new kind of bonding which we wish to term "entropy bonding". Further studies on the structure and properties of the complex are currently in progress.

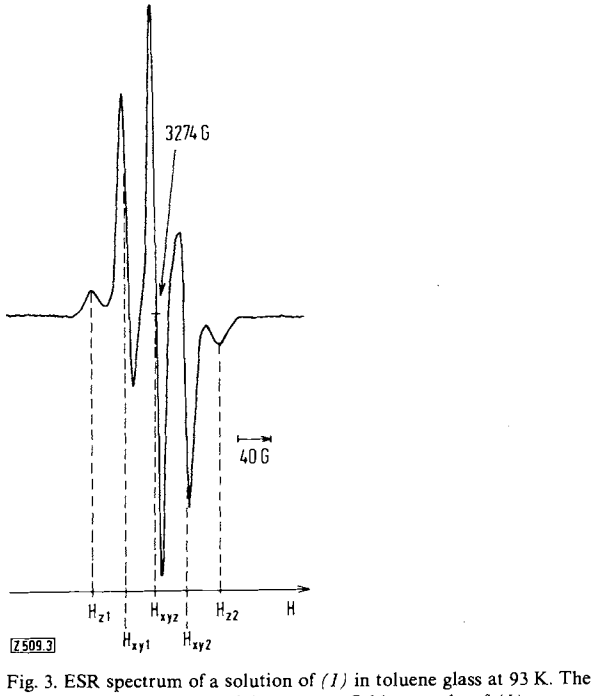


Fig. 3. ESR spectrum of a solution of *(1)* in toluene glass at 93 K. The broken lines indicate the axial resonance field strengths of *(1)*.

At room temperature a solution of the monomeric radical *(1)* in toluene gives a broad, structureless ESR signal. If the solution is cooled to 93 K the solvent solidifies to a glass and a structured ESR signal is observed (Fig. 3) which corresponds to the theoretically predicted signal for randomly oriented quartet radicals having a threefold principal axis of symmetry.

Our interpretation of the ESR spectrum of a three-spin system with magnetic dipole coupling is based on an effective spin Hamiltonian[11]:

$$\mathcal{H} = g\beta\vec{H}\vec{S} + g^2\beta^2\langle\phi|\sum_{i<j}^{3}\left\{\frac{\vec{S}_i\vec{S}_j}{r_{ij}^3} - \frac{3(\vec{r}_{ij}\vec{S}_i)(\vec{r}_{ij}\vec{S}_j)}{r_{ij}^5}\right\}|\phi\rangle \qquad (2)$$

where $\vec{S}$ = total electron spin operator of the three-spin system having the cartesian components $\vec{S} = (S_x, S_y, S_z)$; g = isotropic g tensor; β = Bohr magneton; $\vec{H}$ = external magnetic field; $\vec{S}_i$ = spin operator of electron i, in units of $\hbar$, $\vec{r}_i = (x_i, y_i, z_i)$ space coordinates of electron i; $\vec{r}_{ij} = \vec{r}_i - \vec{r}_j = (x_{ij}, y_{ij}, z_{ij})$, interelectronic vector; $\phi = \phi(\vec{r}_1, \vec{r}_2, \vec{r}_3)$ antisymmetric spatial portion of the quartet state wave function. By proper choice of a molecular coordinate system[11], the operator (2) can be written in the form

$$\mathcal{H} = g\beta\vec{H}\vec{S} + D(S_z^2 - \tfrac{5}{4}) + E(S_x^2 - S_y^2) \qquad (3)$$

with

$$D = \tfrac{3}{4}g^2\beta^2\langle\phi|\frac{r_{12}^2 - 3z_{12}^2}{r_{12}^5}|\phi\rangle$$
$$E = \tfrac{3}{4}g^2\beta^2\langle\phi|\frac{y_{12}^2 - x_{12}^2}{r_{12}^5}|\phi\rangle \qquad (4)$$

For a molecule whose z axis is a threefold axis of symmetry $E = 0$[11].

The operator *(3)* splits the degenerate quartet states. A first order perturbation treatment yields the following axial resonance field strengths:

$$\left.\begin{aligned} H_{xy1} &= H_o - D' \\ H_{xy2} &= H_o + D' \end{aligned}\right\} \quad \vec{H} \perp z$$
$$\left.\begin{aligned} H_{z1} &= H_o - 2D' \\ H_{z2} &= H_o + 2D' \end{aligned}\right\} \quad \vec{H} \parallel z \qquad (5)$$
$$H_{xyz} = H_o \quad \vec{H} \text{ any orientations with respect to } z$$

where $H_0 = h/(g\beta)$, $D' = D/(g\beta)$, and ν is the frequency of the microwave field $\vec{H}_1 \perp \vec{H}$.

If the random orientation of the molecules, the transition probabilities, and the line broadening are taken into consideration[11], an ESR spectrum is calculated which corresponds to the spectrum observed for *(1)* and whose

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assignment is given in Figure 3. The zero-field parameter $D = 128$ MHz was determined from the distance of H_{z2} and H_{z1}.

Apart from the high-field part of the spectrum considered with ($\Delta m = 1$)-transitions, a half-field transition ($\Delta m = 2$) of lower intensity is also observed at 1637 G. In agreement with theory[11] its absorption maximum lies exactly at $H_0/2$.

Radical *(1)* is the first organic three-spin system for which a quartet ground state has been proved.

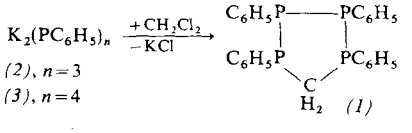
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German version: Angew. Chem. *83*, 1015 (1971)

A Novel Phosphorus Heterocycle: 1,2,3,4-Tetraphenyl-1,2,3,4-tetraphospholane[1]

By *Marianne Baudler, Jürgen Vesper, Peter Junkes,* and *Harald Sandmann*[*]

Several carbon heterocycles containing one or two phosphorus atoms are already known and have been reported[2]. We have been able to synthesize 1,2,3,4-tetraphenyl-1,2,3,4-tetraphospholane *(1)* as the first phosphorus heterocycle of the type $(PR^1)_{n-1}CR^2_2$ ("cyclocarbaphosphanes") derived from the cyclophosphanes $(PR)_n$.

Compound *(1)* is formed in the reaction of methylene chloride with triphenylcyclotriphosphanedipotassium *(2)*[3] or 1,2,3,4-tetraphenyltetraphosphane-1,4-dipotassium *(3)*[4].



The title compound can be prepared batchwise in 73% yield by reaction of pentaphenylcyclopentaphosphane, $(PC_6H_5)_5$, in tetrahydrofuran with the requisite stoichiometric amount of potassium for formation of *(2)* or *(3)* and subsequent treatment of the potassium salt with an equimolar amount of methylene chloride. Compound *(1)* crystallizes from acetonitrile as colorless needles, m.p. 134—138 °C, which are readily soluble in benzene, toluene, and tetrahydrofuran. In the solid state, *(1)* is stable towards atmospheric oxygen for a short while but is rapidly oxidized in the presence of solvents. It could be characterized by complete elemental analysis, osmometric molecular weight determinations, and IR, UV, ^{1}H-NMR, ^{31}P-NMR, and MS spectroscopy[5].

The IR spectrum closely resembles that of pentaphenylcyclopentaphosphane; however, a few characteristic differences are observable in the range 520—300 cm^{-1} (ring-vibration region) and additional absorptions of the CH_2 group occur at 2924 and 2880 cm^{-1} and in the region of the C—H_{aliph} bending vibrations. The UV spectrum [$\lambda_{max} = 215$ nm ($\varepsilon = 37600$) in *n*-hexane] exhibits increased extinction, so additional interactions probably occur between the P atoms *via* d-hybrid functions.

The NMR spectra (solution in CS_2, 24 °C) provide unequivocal evidence of the symmetry of the ring. The ^{1}H-NMR spectrum shows two groups of signals in the intensity ratio 10:1 which can be assigned to aromatic and methylene protons. On decoupling of the ^{31}P nucleus, the multiplet of the methylene protons degenerates to a sharp line at $\tau = 6.970$ ppm, so there is obviously equivalence. The ^{31}P-NMR spectrum consists—with simultaneous proton decoupling—of one AA'BB' system centered at $\delta = -34.6$ ppm (against 85% H_3PO_4, external). These findings are compatible only with C_2 symmetry of the ring. Detailed analysis of the AA'BB' system and X-ray structural investigations are presently being carried out.

The mass spectrum (15 eV) contains a very strong signal due to the molecular ion ($m/e = 446$) alongside one for the fragment $C_6H_5^+$. With increasing electronic energy and heating, additional signals of the following transformation products occur: $(C_6H_5)_4P_2$ ($m/e = 370$), $(C_6H_5P)_3$ (324), $(C_6H_5)_3PCH_2$ (276), $(C_6H_5)_3P$ (262), $(C_6H_5)_2PCH_3$ (199), $(C_6H_5)_2PH$ (186), and $C_6H_5P_2H_3$ (142).

Experimental:

A solution of pentaphenylcyclopentaphosphane (12.5 g, 0.023 mol) in dry tetrahydrofuran (150 ml) is heated under reflux with potassium (3.0 g, 0.077 g atom) for several hours in the absence of air. The reaction mixture is vigorously stirred and reaction allowed to proceed until a clear, dark red solution of *(2)* is formed. A solution of methylene chloride (3.28 g, 0.039 mol) in tetrahydrofuran (20 ml) is then added at 0 °C over a period of 2 hours and the resulting mixture stirred for a further 10 hours. After complete removal of the solvent at reduced pressure, the residue is taken up in carbon disulfide (100 ml), filtered to remove insoluble material, and finally re-evaporated to dryness. Recrystallization of the final residue from acetonitrile (400 ml) affords *(1)* in 73% yield [9.4 g; mol. wt. (osmometric in CS_2, 25 °C): 436].

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Crystal Structure of 2,4-Hexadiynediol[1]

By *Erich Hädicke, Klaus Penzien,* and *Hans W. Schnell*[*]

Numerous derivatives of diacetylene can be polymerized in the crystalline state by heat or high-energy radiation. The main contribution to the understanding of these topochemically controlled reactions[2] has hitherto been the structure determination of polymeric 2,4-hexadiynylene-bis(phenylurethane)[3,4]. We therefore tried to find an explanation for the ready polymerizability of 2,4-hexadiynediol by an X-ray structure analysis of the monomer. The monomeric crystals of 2,4-hexadiynediol, unlike those of 2,4-hexadiynylenebis(phenylurethane), are stable under the employed conditions for an X-ray structure analysis.

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The three-dimensional X-ray structure analysis of 2,4-hexadiynediol was carried out with monoclinic platelets obtained by crystallization from water. Crystallographic data: $a=4.08_9$, $b=15.99_1$, $c=4.76_9$ Å; $\beta=106.5_9°$; $d_{exp}=1.22\,g\,cm^{-3}$; space group $P2_1/c$. The asymmetric unit contains $^1/_2$ molecule $C_6H_6O_2$ ($d_{calc}=1.22\,g\,cm^{-3}$). The individual molecule has a center of symmetry. Owing to their sensitivity to X-rays a number of crystals had to be used in succession for intensity measurements. These measurements on our single-crystal diffractometer ($\vartheta/2\vartheta$-scan, 5-point measurement) were carried out with one crystal as long as periodically repeated measurements on reference reflections showed a statistically significant decrease in intensity. The quality of this crystal was then checked by photography. We recorded 382 reflections of 8 crystals ($Cu_{K\alpha}$ radiation, $\vartheta\leqslant 50°$); 10 of these reflections could not be observed ($I<2\sigma_I$).

Using triple product methods with symbolic addition[5], 96 signs could be determined for the 99 strongest reflections ($E\geqslant 1.0$). An E-Fourier synthesis based on these data afforded the positions of all atoms ($R=50.4\%$). By least-squares isotropic refinement (full matrix) with a scaling factor an R factor of only 25.3% could be obtained. However, simultaneous refinement of the scaling factors from the sets of data obtained from the eight crystals and of the anisotropic temperature factors lowered the R value to 9.4%. The structure of the planar single molecule is shown in Figure 1. The standard deviations of the bond lengths are 0.01 Å, those of the bond angles 0.7°. All bond lengths are in agreement with values given in the literature for similar compounds[6, 7].

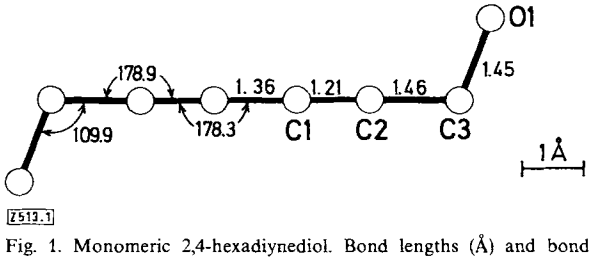


Fig. 1. Monomeric 2,4-hexadiynediol. Bond lengths (Å) and bond angles (°).

If the product in this reaction too (cf. ref. [4]) is a poly-en-yne formed by 1,4-linkage of neighboring monomer units (Fig. 2c), the carbon atoms to be bonded should not be farther apart than about 4 Å[2, 8]. The experimentally obtained intermolecular distances reveal that the monomers can polymerize either along the c axis or along the a/c diagonal. Figures 2a and 2b show the planes fixed by these two directions and the molecular axis.

It is found that the distance between the C atoms to be bound is 3.94 and 3.52 Å, respectively. We therefore assume

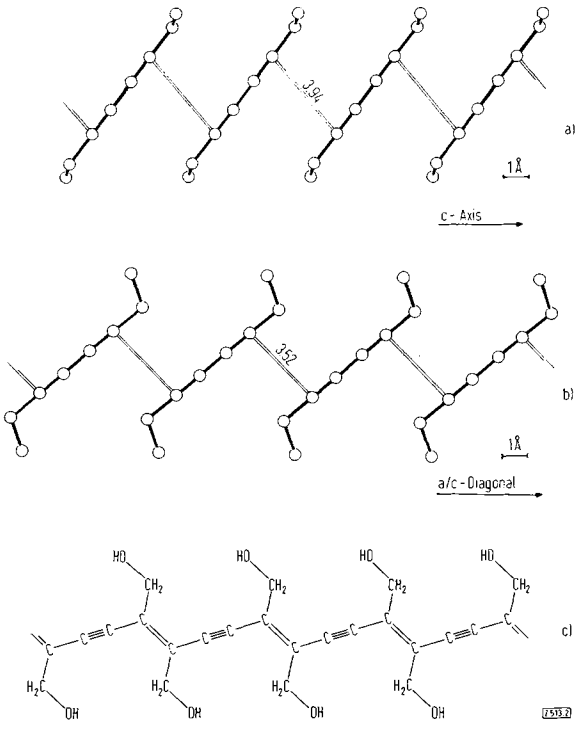


Fig. 2. Possible modes of polymerization of 2,4-hexadiynediol.

that polymerization is possible in both planes; this in turn would account for the largely amorphous character of polymeric 2,4-hexadiynediol.

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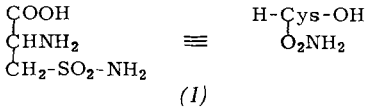
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Synthesis of Modified Amino Acids and Peptides having Anticoagulant, Bactericidal, and Vitamin-K Type Action[**]

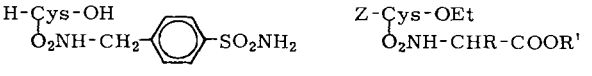
By *Boris Aleksiev*[*]

The known synthesis[1] of cysteinamide (2-amino-3-sulfamoylpropionic acid) *(1)* has been considerably improved[2]. We have been able to synthesize a number of its derivatives[3], including the bacteriostatic Marfanil



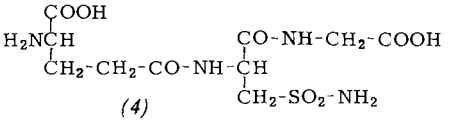
(1)

derivative *(2)*, by reaction of the sulfonyl chloride with amines. Action of amino acid esters on the protected sulfonyl chloride yields compounds *(3)* which are substituted in the sulfonamide group[4].

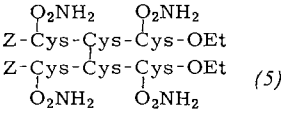


(2) *(3)*

We have also found that the azide and carbodiimide methods can be used with cysteinamide *(1)*[5]; several peptides containing this sulfonamide could be prepared. For example, the sulfonamide derivative of glutathione *(4)* and a hexapeptide of high sulfur content *(5)* were prepared for the first time.

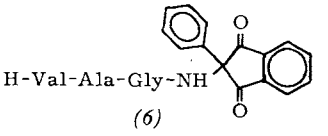


(4)

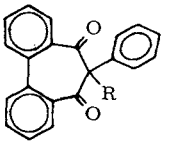


(5)

Another series of modified amino acids and peptides was obtained from 2-amino-2-phenyl-1,3-indandione and 1,3-dioxo-2-phenyl-2-indanacetic acid. The carbodiimide method gave, *inter alia*, the modified tripeptide *(6)* in very good yield[6]. Such compounds can be expected to have an anticoagulant action. In contrast to 2-phenyl-1,3-indandione, its analog *(7)*, synthesized from phenylacetic acid and diphenic anhydride[7], and corresponding derivatives exhibit a powerful vitamin-K type action, resembling that of vitamin K_3[8]. We have prepared a variety of derivatives *(8)* (including amino acid derivatives) of this analog *via* the sulfonyl chloride[9].



(6)



(7), R = H
(8), R = SO_2NHR'

The compounds prepared are currently being tested for physiological activity.

Lecture at Aachen on July 16, 1971 [VB 318 IE]
German version: Angew. Chem. *83*, 986 (1971)

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[**] Abbreviations: Et = ethyl, Z = benzyloxycarbonyl.

Preparation of Dichlorovinylene Carbonate and Examples of its Use in Organic Synthesis

By *H.-D. Scharf*[*]

Treatment of tetrachloroethylene carbonate with zinc leads to dichlorovinylene carbonate *(1)*[1], which can be converted by methanolysis, firstly into methyl methoxycarbonylchloroglycolate *(2)* and subsequently into the dimethyl acetal of methyl glyoxylate *(3)*. Aminolysis with aniline gives α-(*N*-phenylcarbamoyloxy)chloroacetanilide *(4)*, a product analogous to that formed in the first step of the methanolysis[2].

The cheletropic cleavage of *(1)* into oxalyl chloride *(5)* and CO is observable only to a slight extent on prolonged heating of *(1)* under reflux[2]. The loss of CO *via* a concerted linear pathway from the ground state proves to be symmetry forbidden. Thermal [4+2]-cycloaddition of

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(1) to anthracene and its 9,10-dimethyl derivative leads to the cycloadducts *(6)* and *(7)*, respectively, in good yield; *(6)* and *(7)* are converted by hydrolysis into the α-diketones *(8)* and *(9)* respectively. (For an account of the dienophilic reactivity of *(1)* toward 9,10-dimethylanthracene, see Ref. [3].) Acyclic dienes, such as dimethyl-1,3-butadiene, react like 1,3-cyclohexadiene to give only small amounts of the [4+2]cycloadducts *(10)* and *(12)*; with cyclopentadiene, the adduct *(11)* is formed in 65—70% yield. Hydrolysis of the bridged adducts *(11)* and *(12)* also leads to α-diketones *(14)* and *(15)*; hydrolysis of *(10)* affords 3,4-dimethylcatechol *(13)*.

The photosensitized addition of *(1)* to common olefins proceeds in the sense of a [2+2] cycloaddition with formation of the cyclobutane derivatives *(16)*, which on hydrolysis are immediately converted into the α-hydroxycyclopropanecarboxylic acids *(17)*[1,4]. Products *(17)*, which are derived from cyclic olefins, react as tosylates with expansion of the ring.

Surprisingly, *(1)* also undergoes photocycloaddition reactions with benzene[5] and naphthalene[6] to give first 1,2-cycloadducts which subsequently undergo a 1,3 shift yielding derivatives corresponding to the adducts *(6)*. (Naphthalene forms *exo* and *endo* adducts.) Hydrolysis leads to the previously unknown α-diketones.

Lecture at Leverkusen, June 6, 1971 [VB 319 IE]
German version: Angew. Chem. *83*, 987 (1971)

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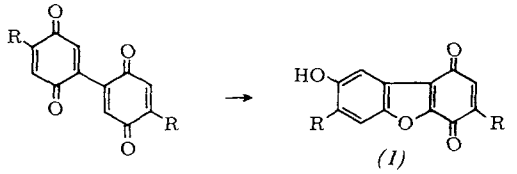
[4] *H.-D. Scharf* and *R. Klar*, Liebigs Ann. Chem. *739*, 166 (1970); *G. Hesse* and *P. Lechtken*, Angew. Chem. *83*, 143 (1971); Angew. Chem. internat. Edit. *10*, 133 (1971).

[5] *H.-D. Scharf* and *R. Klar*, Tetrahedron Lett. *1971*, 517.

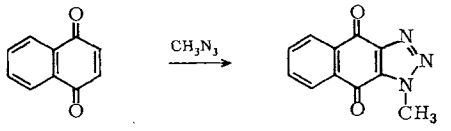
[6] *H.-D. Scharf* and *J. Aretz*, unpublished work.

"Selected Abstracts", a part of the journal previously containing summarized versions of primary publications of topical interest, will in future be devoted exclusively to abstracts of publications of a more comprehensive nature (reviews, progress reports, *etc.*). The editorial staff will make every effort to ensure that this modification of the "Selected Abstracts" section will provide readers of "Angewandte Chemie — International Edition" with an even more representative and up-to-date survey of current developments in each of the branches of chemistry than heretofore.

The synthesis of heterocyclic quinones is discussed by *I. Baxter* and *B. A. Davis*, only those quinones being considered that contain the hetero ring fused directly to a quinone moiety. Examples of heterocyclic systems are furan, pyrane, dioxane, thiophene, dithiane, dithiole, pyrrole, pyrazole, imidazole, triazole, pyridine, diazine, oxazole, or oxazine. A number of such compounds are used as dyes, catalysts, or drugs. Some antibiotics such as



(1)



(2)

streptonigrin and the mitomycins are heterocyclic quinones. They can nearly all be prepared by oxidation of derivatives of the parent compounds carrying OH or NH_2 substituents. The syntheses of *(1)* and *(2)* can be regarded as examples of intramolecular cyclization and 1,3-dipolar addition respectively. [Synthesis of Heterocyclic Quinones. Quart. Rev. Chem. Soc. *25*, 239—263 (1971); 108 references]

[Rd 419 IE –E]

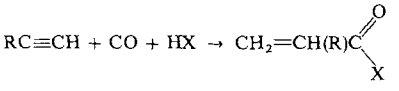
Resolution of racemates into enantiomers is summarized by *P. H. Boyle*. Reactions of racemates with chiral reagents are known to yield diastereomers which are physically separable. More recent reagents of this kind are, *e.g.*, 1-phenylethylamine, dehydroabietylamine, *threo*-1-*p*-nitrophenyl-2-aminopropane-1,3-diol, tartranilic acid, and menthylchloroformate. The kinetic methods of resolution are based on differences in reaction rates of the two enantiomers with chiral compounds. Thus reaction with diisopinocamphenylborane is suitable for the separation of alkenes having no functional groups. Other possibilities include reduction with chiral compounds or with microorganisms, chromatography and ion exchange. The most important reagent for resolution by formation of molecular complexes is 2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid. Resolution by seeding of solutions is of industrial interest. [Methods of Optical Resolution. Quart. Rev. Chem. Soc. *25*, 323—341 (1971); 132 references]

[Rd 422 IE –E]

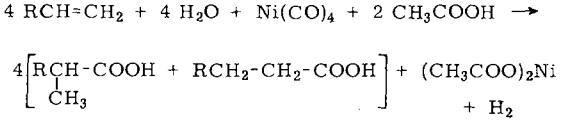
Concepts of liquid water structure are reviewed by *P. Krindel* and *I. Eliezer*. Many different models are presented, and their utility in contributing to an understanding of the known properties of liquid water is evaluated. The relevance of X-ray scattering and vibrational spectroscopy to the problem is stressed. In addition, brief accounts of "anomalous" water and of interfacial effects are included. [Water structure models. Coord. Chem. Rev. *6*, 217—246 (1971); 137 references, 12 figures, 4 tables]

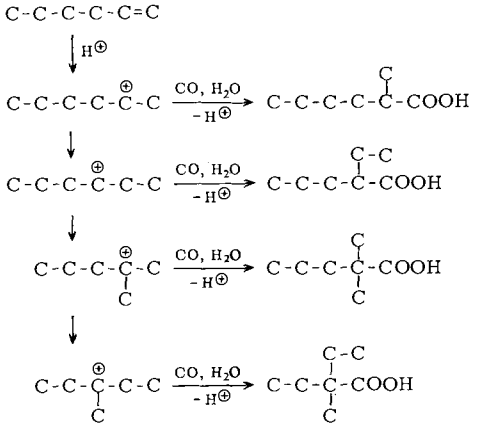
[Rd 425 IE –H]

Catalytic carbonylation of alkenes and alkynes with carbon monoxide is reviewed by *Yu. T. Eidus*, *K. V. Puzitskii*, *A. L. Lapidus*, and *K. Nefedov*. The alkynes are carbonylated in the presence of a Group VIII metal carbonyl and a compound having a mobile H atom:



stoichiometric or catalytic amounts of carbonyl are used. The carbonylation of alkenes can be carried out a) in the presence of catalysts based on Group VIII metals or





b) with acid catalysts. [Carbonylation of Mono-Olefinic and Mono-Acetylenic Hydrocarbons. Russ. Chem. Rev. *40*, 429—440 (1971); 237 references]

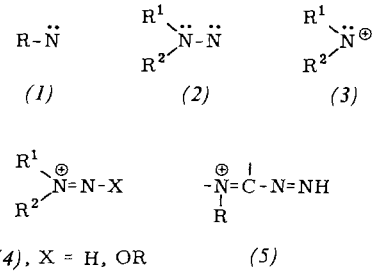
[Rd 426 IE –M]

Progress in use of amino acid mixtures in place of proteins for human nutrition in the past decade is discussed in a review by *V. M. Belikov* and *T. L. Babayan*. Prolonged administration of such mixtures shows that they are an

adequate substitute for nutritional proteins and that no side effects occur. Moreover, such mixtures can be used for improving second class proteins. The authors discuss the nitrogen balance and biological value of proteins, amino acids, and their mixtures, and also the reasons for variations in the degree of utilization of proteins and amino acid mixtures; in conclusion they turn their attention to amino acids in medicine, concentrating particularly on parenteral administration. [Mixtures of Amino Acids in Human Nutrition. Russ. Chem. Rev. *40*, 441—445 (1971); 164 references, 6 tables]

[Rd 428 IE -M]

The chemistry of reactive nitrogenous intermediates is the topic of an article by *S. Hünig*. The author deals mainly with the production and subsequent reactions of uncharged and cationic intermediates having a sextet of electrons on the nitrogen. Nitrenes *(1)*, 1,1-disubstituted diazenes *(2)*, nitrenium ions *(3)*, 1,1-disubstituted diazenium ions *(4)*, and phenylogous and azavinylogous diazenium ions *(5)* receive particular attention. [Aus der Chemie reaktiver



(1) *(2)* *(3)*

(4), X = H, OR *(5)*

stickstoffhaltiger Zwischenstoffe. Helv. Chim. Acta *54*, 1721—1747 (1971); more than 100 references]

[Rd 429 IE -M]

BOOK REVIEWS

Catalyse et catalyseurs en chimie organique (Catalysis and Catalysts in Organic Chemistry). By *P. Brun*. Masson et Cie, Paris 1970, 1st ed., 241 pp., 29 figures, Fr. 70.—.

The use of catalysts in organic reactions has received comparatively scanty treatment in previous textbooks on heterogeneous catalysis. The attempt of the present book to repair this deficiency is therefore welcome. The book starts with a section on methods for the investigation of surfaces and on the underlying phenomena which play a part in catalysis; this is followed by a section on the role of individual chemical elements in catalysis. After a discussion of the properties required for technical purposes, reactions such as hydrogenation, oxidation, dehydrogenation, hydration, dehydration, rearrangements, polymerization, and also the influence on radicals and many other topics are discussed.

Although the plan of the book is good, its execution leaves much to be desired. Conciseness in presentation should not be achieved at the expense of comprehensibility, but this occurs frequently, particularly in the first chapter. On the basis of the descriptions given there no-one could understand the BET method of surface area determination or the measurement of a pore spectrum, or even carry them out. The bibliography should be just as complete as the collection of reactions; if, however, one averages out the years of appearance of the papers quoted, values prior to 1940 are obtained in some cases. It is therefore not surprising that one looks in vain for many reactions at the forefront of current interest (oxidation of ethylene on silver to ethylene oxide; oxidation of propylene to acrolein, butene to butadiene, and the ammoxidation of propylene to acrylonitrile on bismuth-molybdenum catalysts). On the other hand, it is pleasing to find the catalytic reactions of complicated organic molecules handled in previously unknown detail.

Willi Herzog [NB 995 IE]

Chemische Technologie (Chemical Technology). Edited by *K. Winnacker* and *L. Küchler*. Carl Hanser Verlag, Munich 1969. 3rd ed., Vol. 1: Anorganische Technologie I (Inorganic Technology I), xx, 729 pp., 271 figures, 137 tables, bound, DM 168.—. Vol. 2: Anorganische Technologie II (Inorganic Technology II), xxiii, 671 pp., 267 figures, 138 tables, bound, DM 168.—.

This established collective work gives in a limited space a description of the individual branches of the chemical industry. The editors' efforts to keep the size within limits can be clearly seen: despite complete rewriting, many of the articles have the same number of pages as in the previous edition. Even the bibliographies have not just been amplified by the addition of new references but have been critically reviewed, so that in places they are in fact shorter than before. Some of the articles are completely new, which has suggested a regrouping of the whole material. For this reason, although the individual volumes of the third edition have the same number of pages, or even fewer than before, the whole work will consist of seven volumes, while the previous edition consisted only of five.

Volumes 1 and 2, which have now appeared, deal only with inorganic technology, in contrast to the previous editions. The review articles on process technology and chemical reaction techniques, which previously were at the start of the entire work, will now appear in Volume 7 ("General").

Volume 1 starts with an new contribution, "Lines of development of chemical technology", by *Winnacker* and *Biener*, which provides an excellent introduction to the descriptive articles that follow. The stages of the short history of the German chemical industry are clearly shown and set in an international context. The particular problems of research are discussed, as also are those of patent technology and documentation.

In the other articles an attempt has been made to adapt the material so that related topics are brought together. Over half of the 35 principal authors are subject specialists who are new to this task. This, and the consideration of recent developments, has led to considerable changes in places.

The overall field is broken down into the following articles:

Volume 1: Lines of development of chemical technology (*Winnacker* and *Biener*, 45 pages); Water (*Greiner*, 31 pages); The potassium industry (*Autenrieth*, 85 pages); Technology of boron compounds (*Heinerth*, 12 pages); Common salt, soda, and potash (*Heuse* and *Wilsing*, 51 pages); Chlorine and its inorganic compounds (*Hund* and *Zirngiebl*, 97 pages); Fluorine and its inorganic compounds (*Weise*, 17 pages); Phosphorus and its inorganic compounds (*Harnisch* and *Saenger*, 79 pages); Carbide, calcium nitride, and silicon carbide (*Ritter* and *Krause*, 40 pages); Electrolytic graphite and artificial carbon (*Dönges* and *Vohler*, 47 pages); Peroxo compounds (*Pistor*, 81 pages); Nitrogen and its inorganic compounds (*Mundo*, 117 pages).

Volume 2: Sulfur and its inorganic compounds (*Dönges*, *Saenger* and *Wolf*, 84 pages); Chromium compounds (*Dilthey* and *Weise*, 35 pages); Manganese compounds (*Preisler*, 19 pages); Inorganic pigments (*Hund* and *Schultz*, 53 pages); Rare earths (*Greinacher*, 29 pages); Binders in building work (*Wittekindt*, 56 pages); Ceramics (*Kienow*, 60 pages); Glass (*Trier*, 65 pages); Liquefaction and separation of gases (*Baldus*, *Knapp* and *Schlatterer*, 101 pages); Materials of high surface area (*Bratzler*, 46 pages); Problems of chemical technology in nuclear technology (*Küchler*, 93 pages).

There is no need to read further than the article on water to see how favorable an influence the new treatment can exert on both form and content. However, it is surprising that waste water purification is no longer dealt with in a separate section. In this connection, the question arises whether air, which like water is used as a raw material and as a coolant and is burdened with waste materials, does not deserve a more thorough treatment than it receives in the article on gas separation.

All the articles on classical inorganic technology have been rewritten and brought up to date as far as possible. Statistical data and literature references are considered up to 1968. New developments have caused large changes, particularly in the electrochemical processes used in chlorine chemistry. The articles on graphite and on nuclear technology are new.

From the earliest days graphite electrodes have been of decisive importance in the great electrochemical and electrothermal processes of inorganic chemistry. The arrival of more and more new applications, particularly in apparatus construction, in nuclear technology, and most recently in the field of fibers, justifies the treatment of this topic as a subject in its own right.

Nuclear technology is beginning to make a significant contribution to power supplies, and it is high time that is was included in the normal realm of technology. From the production of fissionable material with the use of minimum separation factors to the performance of radiochemical reactions in chemical nuclear reactors and the processing of nuclear fuels under conditions necessitating extreme purity and safety requirements, many problems of chemical technology are involved. *Küchler* and his associates have summarized them very successfully.

It is a difficult task to cover so vast a field as that of inorganic chemistry while on the one hand presenting a comprehensive picture and on the other hand preserving the unity of the presentation by keeping it as far as possible to a limited space. The participation of a large number of authors may lead to a sharing but not a simplification of this task. The editor and publisher have overcome the problems with great success in the first two volumes of the third edition of this work. It is to be hoped that the remaining volumes will soon be published, so that the complete work can take its place in our libraries.

Ulrich Wagner [NB 997 IE]

Thermal Stability of Polymers, Vol. 1. By *R. T. Conley*. Marcel Dekker Inc., New York 1970. 1st ed., x, 644 pp., numerous figures, bound $ 44.50.

The two-volume work, which is being published in the series "Monographs in Macromolecular Chemistry", and of which this is the first volume, reviews the most important literature on heat-resistant plastics.

The opening chapters are devoted to the polymer properties and the structural characteristics that influence the thermal stability of polymers. The broad concept of the "thermal stability" of polymers is first explained and discussed with reference to general criteria such as molecular structure and crystallinity, kinetics and mechanism of the thermal depolymerization, the basic theory of random degradation processes, and fundamental problems relating to oxidation products. Separate chapters are devoted to the thermal or oxidative degradation of various important classes of substances, *e.g.* polyolefins, rubber, vinyl and vinylidene polymers, polyfluorohydrocarbons, polyamides, polyesters, polyethers, formaldehyde-based thermosets, epoxy resins, cellulose derivatives, and some heterocyclic ring systems. The last chapter deals with inorganic polymers based on boron, silicon, phosphorus, and sulfur. The possible reactions of the various classes when heated in the presence and in the absence of oxygen are discussed in detail.

Since the book draws on the specialized experience of several authors, it cannot and does not claim to be complete in its coverage of polymers and to give equal treatment to all. The present first volume unfortunately contains no table of contents for Volume 2, which is in preparation. Consequently, no final judgment can be made on this point at present.

The keyword index is regrettably not sufficiently comprehensive, since many of the facts and classes of substances treated are mentioned only superficially. For example, polysulfides are mentioned on p. 181, but do not appear in the subject index. More information on the practical use of members of the classes of substances discussed and of the effects described would have been of special interest to the industrial chemist.

A few technical shortcomings must be mentioned. Temperatures in °C and in °F are indiscriminately mixed. As a result of many errors, *e.g.* missing or displaced double and single bonds and H atoms, as well as tetravalent phosphorous or tetravalent boron, some of the formulas are almost incomprehensible.

Despite these faults, the book should be of use to any chemist who is concerned with the degradation of polymers and who requires information beyond that normally available.

Rudolf Merten [NB 1000 IE]

Fluorescence Analysis. By *C. White* and *R. J. Argauer*. Marcel Dekker Inc., New York 1970. 1st edit., x, 389 pp., numerous figures, bound, $ 18.75.

During the past two decades fluorescence analysis has become a favorite analytical technique, which has proved particularly useful in biological, biochemical, and clinical laboratories. This is due to its ability to detect a large number of substances, which either themselves fluoresce or else can be converted into fluorescing compounds by specific reactions, in astonishingly small concentrations, and at a relatively modest cost in equipment.

The present monograph is concerned with the currently available instruments and techniques. The basic phenomena of fluorescence, the currently available spectrofluorimeters, calibration methods, and fluorescence standards are all dealt with briefly but in sufficient detail for routine applications. The fluorescence properties of metal chelates are presented in great detail, since these form the foundation of the whole technique. There are further detailed chapters devoted to the fluorescence of proteins, vitamins, and steroids, and, rather outside the scope of the present book, chapters on chemiluminescence and X-ray fluorescence. Some criticism concerns the chapter on fluorescence indicators; the authors do not appear to know that the changes in a fluorescence spectrum are not necessarily governed by the pH value.

The emphasis of the book is on applications. Since it contains material reprinted from the manuals of two manufacturers it contains a large number of detailed instructions for use in a wide range of applications, particularly for clinical chemistry. The detailed nature of the presentation and the lack of theoretical padding make this book appear particularly suitable for the instruction of laboratory technicians.

Theodor Förster [NB 999 IE]

Grenzflächenaktive Substanzen (Surface Active Substances). By *H. Bueren* and *H. Grossmann*. Chemische Taschenbücher Vol. 14, edited by *W. Foerst* and *H. Grünewald*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971. x, 196 pp., 64 figures, 27 tables, paperback DM 24.—

The present pocket book is an attempt by the authors to fill a gap in the technical and scientific literature with a brief survey of everything that is worth knowing about surface active substances. The subject is discussed under the following headings: historical review, scientific importance, physico-chemical principles, chemical composition of surface active substances, analysis, biological degradation, industrial use.

The book will be a valuable aid to the interested student who wishes to find out more about the field than he can learn from chemistry and technology lectures and to the practical worker in adjacent fields who wishes a quick survey. The large bibliography attached to each chapter also offers an opportunity to pursue the study further by reference to the original literature.

A number of adverse comments are also justified. Too much emphasis is sometimes placed on practical use, at the expense of chemical and industrial aspects (as in the case of nonionic surfactants). The treatment of the physico-chemical principles of surface activity is rather too general and simplified. No mention is made of some important current developments in the surfactant field, such as new classes of surfactants and the substitution of detergent phosphates. There are a number of printing errors in the text and several omissions in tables and graphs, some of which lead to distortion of meaning, and which will have to be corrected in later editions.

Apart from these points, the authors have succeeded well in their purpose of presenting a general survey of the field of surface active substances.

Horst Baumann [NB 10 IE]

Wörterbuch der Chemie und der chemischen Verfahrenstechnik (Dictionary of Chemistry and Chemical Engineering), Vol. 1 German/English. By *L. de Vries* and *H. Kolb* with the collaboration of *J. Thuss*. Verlag Chemie GmbH, Weinheim/Bergstr., and Academic Press, New York–London, 1970. viii, 708 pp., bound, DM 135.—.

The 70000 or so entries in this technical dictionary have been drawn from the whole field of chemistry and also from the vocabulary of chemical engineering, metallurgy, and the petroleum, rubber, and textile industries. The dictionary also contains terms from the fields of physics, biology, medicine, mathematics, mineralogy, and crystallography. The authors have taken particular trouble to include recently coined terms from biochemistry, physiology, molecular biology, biophysics, atomic physics, spectroscopy, stereochemistry, reactor engineering, and electronics. Chemical compounds are recorded both under their trivial and under their systematic names, although naturally only the simple compounds are included. Outmoded names still often found in the technical literature will be found, but are specially marked. At the end there is a table of the chemical elements, a table of German weights and measures, and a temperature-conversion table.

This dictionary has been used by us ever since it appeared and has rarely failed to supply an answer. There is thus no doubt that this is an extremely useful work, and not only to chemists but also to engineers and technical translators.

If we consider the sheer bulk of the material handled, it is hardly surprising that, despite the great care with which the book has been compiled there are still a few minor errors. For example, "Rotkupfererz" is only given under "Cuprit"; omissions include Widerstandszahl (drag coefficient), Schüttschicht (fixed bed), Formkern (mandrel), the synonym for film evaporation (film boiling), and under Verweilzeit the English term "residence time". Outmoded names for compounds are not always marked, *e.g.* "Zinnjodür". Neither descriptions such as "Zirkon" for Zr and "Vanadium" for V nor the spellings "Siliciumkarbid" and "Silikat" are in agreement with the principles of nomenclature, and there seems to be some confusion about the spelling of "oxid" (oxidhaltig, but oxydartig), although particular mention of this is made in the foreword. Since, however, the entire vocabulary is stored on magnetic tape, future modifications should not cause any difficulties.

It should be emphasized that these minor blemishes in no way detract from the work's usefulness, and it is hoped that this dictionary will find the widest possible circulation.

Christian Weiske [NB 9 IE]

Methoden der enzymatischen Analyse (Methods of Enzymatic Analysis). Edited by *H. U. Bergmeyer*. Verlag Chemie GmbH, Weinheim/Bergstr. 1970. 2nd Edit., lxix, 2220 pp., numerous figures, bound DM 285.—.

The second edition of this work has now appeared, and one need only look back to the reviews of the first edition[1] to see that any further praise would be superfluous. Then, as now, no comparable work existed, and all that remains for the reviewer to do is to indicate the places where this new edition (edited by *H. U. Bergmeyer* with the collaboration of 230 authors) is an improvement on the original one.

The new edition of this laboratory handbook is essentially larger and in two volumes. Despite the fact that it has almost doubled in size, the presentation is clearer, and the information provided is more precise and more markedly oriented toward practical use in clinical and biochemical laboratories. The care that has been taken in the layout of the book is one of the fundamental factors contributing toward its clarity.

The general division of the material into four sections has been retained; however, the general introduction is now followed by biochemical reactions as the second section, then come the methods for measuring enzyme activity, and finally the methods for the determination of metabolites. The general introduction has been extended to nine times its original length and has assumed an entirely new character. In addition to the description of new analytical methods, such as the enzyme isotope dilution technique, and information on the automation of analyses, the clinician will find valuable practical help in the newly added chapter "Evaluation, Checking, and Assessment of Measurements". Stability properties of substrates, enzymes, and tissue cultures are carefully described and illustrated by numerous literature references.

Biochemists who work with enzymes will note with gratitude that in the section on "Biochemical Reagents" not only are more than a hundred of the best known enzymes grouped together with their properties, but also the procedures for their activity determinations are given. In this connection it would be desirable if in future this part could also be arranged according to the rules of IUPAC nomenclature, as has already been done in the section on "Measurement of Enzyme Activities". Here account is taken of the mechanization and automation of enzyme analysis in clinical laboratories, a phenomenon that is observed more and more these days. With the determination of GOT, GPT, and LDH as examples, detailed data on automated analysis are given, and for other enzymes largely mechanized analyses are described. Analyses by electrophoretic separation, radiochemical analysis, and to a greater extent fluorometric methods are given for the first time, in addition to the traditional methods. Thus, for example, 41 pages are devoted to LDH and its isoenzymes, seven analytical methods and four methods of automatic analysis are given, and 51 literature references are provided to ensure the availability of further information. The favored subdivision into necessary reagents, solutions, method of operation, *etc.*, has been extended to include data on the precision of the method and also pipetting schemes which will lead to a dramatic simplification of the actual execution of determinations. The new edition no longer contains the chapter on histochemical methods, and in our opinion rightly so, since such methods are described in the appropriate textbooks and handbooks on histochemistry.

In both the section on the determination of enzyme activity and the final section on methods for metabolites, each determination is prefaced by a brief introduction and the sensitivity and precision of the method are given. Particular emphasis is placed on the pipetting scheme with data on the concentrations in the test. The methods given for the production of preparations of enzymes not commercially available are very useful. Finally, the tables giving the metabolite contents of animal tissues deserve particular mention, since they represent a valuable compilation of previously published values.

All things considered, this book, which has already made a name for itself, is indispensable to all practising biochemists, and is a practically inexhaustible source of information for laboratory practice. It is sure to find a wide distribution and to be highly popular.

Dieter Oesterhelt and *Feodor Lynen* [NB 13 IE]

[1] Cf. Angew. Chem. internat. Edit. *2*, 52 (1963).

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SC = Short communication LA = Literature abstract
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